THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—48TH YEAR SYDNEY, SATURDAY, AUGUST 19, 1961 No. 8

Table of Contents

ORIGINAL ARTICLES— Page

Current Problems in Gastric Surgery, by Daniel Lane .. 289
Treatment of Gastric Cancer, by J. Grayton Brown 297
Gluten-Free Diets in Australia, by Theo Cooke .. 298
Serum Glutamic Oxaloacetic Transaminase (S.G.O.T.) in the Diagnosis and Prognosis of Myocardial Infarction, by R. W. Beal 301
Serum Protein Values in New Guinea Highland Natives, by Jekabs Kariks 305
The Effect of Vitamin A and Vitamin D Capsules upon the Incidence of Coronary Heart Disease and Blood Cholesterol, by F. C. H. Ross and A. H. Campbell 307
Embolectomy and Retrograde Flush: Consideration of the Reasons for an Aggressive Attack on Acute Thrombo-Embolism, by Walter Burfitt-Williams 311

REPORTS OF CASES—

Neonatal Jaundice: Two Cases Associated with Glucose-6-Phosphate Dehydrogenase Deficiency in Erythrocytes, by Charles Lee, Arnold Tink, Helen Robin, and John Harley 315
Gynæcomastia and Multiple Myeloma, by J. E. Gault 318
Case of Milk Allergy, by Helen B. Wiles 320
Nocardiosis: Report of a Case Resembling Sporotrichosis, by A. Baumgarten 321

REVIEWS—

Clinical Disorders of the Pulmonary Circulation .. 323
Surgical Treatment of Unequal Extremities 323
The Rickettsial Diseases 324
The Principles of Surgical Nursing 324

BOOKS RECEIVED 324

LEADING ARTICLES—

Stirring of the Academic Waters 325

COMMENTS AND ABSTRACTS—

Poliomyelitis in an Immunized Community 327
Neural Integration in Systemic Pathology 328
Shorter Abstracts: Hygiene 328

ON THE PERIPHERY— Page

The Preservation of History 330

OUT OF THE PAST 330

SPECIAL CORRESPONDENCE—

London Letter 330

CORRESPONDENCE—

The Use of Unmodified Blood Given by Direct Transfusion 331
The Hyperventilation Syndrome 332
The Composition of Fluids for the Care of Patients with Abnormal Electrolyte Situations 332
Physician, Protect Thyself! 333
An Australian Medical Association 333

POST-GRADUATE WORK—

The Melbourne Medical Post-Graduate Committee 333

UNIVERSITY INTELLIGENCE—

University of New South Wales 334
The University of Adelaide 335

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA 335

NOTES AND NEWS 336

CORRIGENDUM—

The Management of Maldescended Testis 336

DEATHS 336

DIARY FOR THE MONTH 336

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 336

EDITORIAL NOTICES 336

CURRENT PROBLEMS IN GASTRIC SURGERY.[1]

By DANIEL LANE, M.B., F.R.C.S. (Eng.), F.R.C.S. (Edin.), F.R.A.C.S.,

Department of Surgery, Mater Hospital, Brisbane.

There is nothing which persevering effort and unceasing and diligent care cannot overcome.

—SENECA.

In attempting to review some problems in gastric surgery which still confront us, I am very mindful of the great advances which have been made during recent years.

The younger generation of surgeons who are interested in this branch of work have witnessed many changing trends in the surgery of the stomach and duodenum during the past 10 years. However, the challenge of further improvement remains.

[1]Based on a paper delivered during the Mater Hospital Week during Jubilee Year, 1960.

My comments are based largely on personal observation, but I must pay tribute to my surgical mentors both in Brisbane and London, who have held my hand and showed the way. To them I dedicate this short paper, and hope that I, in turn, may have advanced a little along the path of surgical learning and achievement.

Modern Surgical Treatment of Duodenal Ulcer.

I suppose that most surgeons who practise gastric surgery will admit that one of their major problems is the loss of weight, sometimes considerable, which often ensues after partial gastrectomy. For this reason, we continue to seek the ideal operation for peptic ulcer, especially duodenal.

From my observations it is apparent that there can be no ideal operation, because there is no ideal patient or stomach. If we take notice of the work of Card and his associates of Edinburgh (1959), then we should be able to decide, by a pre-operative maximum-tolerance histamine test, the extent of gastrectomy required, but, of course, we must admit that some people are simply not suitable for such a radical operation as subtotal gastrectomy. For them the answer would be readily supplied by Burge

(1960), in selective vagotomy (which should be proven complete by electrical stimulation via an inflated gastric tube) and gastro-enterostomy.

Tanner (1960) has suggested that if partial gastrectomy is to be avoided, then complete vagotomy combined with anterior juxta-pyloric gastro-enterostomy will produce good results in about 92% of cases.

However, as Goligher indicated at the Royal Australasian College of Surgeons meeting in Adelaide (1960), so far it has been impossible to compare the results of the various operations suggested for duodenal ulcer owing to the selection of cases and the type of operation which is so often influenced by the personal bias of the surgeon concerned (Figure I).

We must be prepared to vary the type of our operation to suit the patient or his stomach, and, in general, we are becoming very much more conservative.

Burge (1960) has shown the value of selective vagotomy with preservation of the cœliac branch of the posterior vagus nerve. From my experience of this procedure, the troublesome post-vagotomy diarrhœa, which one sometimes encountered following standard vagotomy, is no longer a problem (Figures II and III).

Although we have many varieties of operation to choose from, I feel that a well-done partial gastrectomy, performed according to the dictates of an expert such as Tanner, is usually followed by a good result. However, selective vagotomy and gastro-enterostomy provide a sound alternative. There will always be a certain small proportion of patients who will complain of post-operative symptoms, but even the majority of these are prepared to admit the value of the procedure when the post-operative symptoms are compared with the symptoms prior to operation.

Special Problems in Gastric Ulcer.

The management of gastric ulcer is much more straightforward than that of the duodenal ulcer. My main thoughts on this subject are directed to the giant gastric ulcer, the very high lesser-curve gastric ulcer, and the undue prolongation of medical treatment of gastric ulcer.

As Strange (1959) emphasized, most giant gastric ulcers prove to be benign, contrary to what most of us have been taught. I have rarely seen at operation a malignant giant gastric ulcer (that is, with a diameter of at least 3 cm.) (Figure IV).

The fact that many of these ulcers occur in a late age group must make us more circumspect in the surgical management, as we can expect a higher mortality rate than is usual.

Some of these ulcers, especially those on the lesser curvature, can present with pyloric stenosis. In some cases, the explanation lies in the fact that recurrent ulceration of the lesser curve causes shortening of the lesser curve, and as a result the stomach does not empty in a normal fashion.

The very high lesser-curve ulcer should be treated conservatively, owing to the technical difficulties involved at operation and also because of the rarity of malignant change. Occasionally one is obliged to operate, in which case the Pauchet method of resection becomes essential, but great care must be taken to avoid causing obstruction of the œsophageal inlet.

I am afraid that surgeons still see gastric ulcers that have been in the hands of physicians far too long (Figure V). As a result, malignant change and pancreatic disorders still occur unnecessarily. Much of this reluctance on the part of physicians to hand over their gastric problems is no doubt due to the memory of the many post-gastrectomy cripples whom they have been obliged to treat in the past. We hope that this memory will soon fade.

The Perforated Ulcer.

In 1952 I commenced treating selected patients with perforated ulcers by immediate gastrectomy. I have had no reason to change my opinion that this is a most rewarding procedure. The mortality is as low as that of simple closure and the disease is usually cured by a single operation. Of course, I can speak only for such surgery performed under ideal conditions in our major hospitals.

I would certainly try to avoid any radical operation in the young subject with a small acute perforation, but even then, cases arise when the more radical operation seems justified.

The following case illustrates the problem involved.

A male patient, aged 31 years, was admitted to hospital on April 2, 1960. He claimed that while drinking beer he had experienced sudden, severe pain in the upper part of the abdomen. He had apparently suffered indigestion after meals for many years, and pain often woke him at night. He had had two previous hæmatemeses. A barium-meal X-ray examination performed in the previous year had revealed no abnormality. His general practitioner volunteered the information that the patient drank heavily and was most unreliable in observing the ulcer therapy prescribed. Examination revealed the typical rigid abdomen of a perforated peptic ulcer; this diagnosis was confirmed by immediate laparotomy. The patient was found to have a small perforation on the anterior wall of the pylorus. Immediate partial gastrectomy and selective vagotomy were performed. The patient's recovery was uneventful.

Simple closure of a perforation is to be recommended for general purposes, but the longer we follow up these patients the more we realize that it is rarely followed by complete healing of the ulcer.

Thus I feel sure that immediate partial gastrectomy with or without vagotomy will continue to gain popularity for the treatment of the perforated ulcer.

Stomal Ulcer.

This is a problem which seems to be far less common than formerly, no doubt because of our better understanding of peptic ulcer surgery and its pitfalls.

Whenever we see a patient who complains of persistent pain following partial gastrectomy or gastro-enterostomy, whether it be months or years after the original operation, we must consider the possibility of stomal ulcer.

The great problem is in the diagnosis, and even if repeated X-ray studies fail to show any definite ulcer, we must still harbour the idea lest we fall into the grievous error of making a diagnosis of functional pain.

These ulcers are particularly difficult to demonstrate radiologically, and for this reason we must give the radiologist every assistance by providing an adequate clinical history and description of previous operations.

What is the treatment? I think that our ideas are now well formulated with vagotomy as the keystone in treatment. If previous gastro-enterostomy has been performed, then Polya gastrectomy should be combined with vagotomy. If the stomal ulcer has followed partial gastrectomy, then excision of the ulcer (with or without further gastric resection) plus vagotomy seems the best solution.

There is always the odd case of stomal ulcer which continues to recur; such cases have been recorded in the literature on various occasions. In this circumstance we are advised to search for an islet-cell tumour of the pancreas which, in some unknown way, causes intense gastric hypersecretion (Zollinger-Ellison syndrome).

The Dumping Syndrome.

This problem is still with us, and so long as we continue to violate the security and control of an intact pyloric sphincter, it would seem that we must accept it as a small price to be paid for the tremendous gains in modern gastric surgery.

There is no doubt that any study of the great problem of weight loss after gastrectomy traverses the sphere of the so-called dumping syndrome. Why some patients dump and other do not is an enigma in the majority of cases. It would seem that, leaving technical faults aside,

there is a susceptibility on the part of some patients to suffer the syndrome which we have labelled dumping, for want of a better name. Although it is encouraging to know that most of the symptoms improve or disappear with the passage of time, a small group of patients with obstinate dumping (5% or less) remains to haunt us. What of them?

Le Quesne and his colleagues (1960) have attempted to provide an answer. They suggest that in certain susceptible patients, carbohydrate in the diet is particularly liable to cause symptoms because of its rapid breakdown into glucose molecules and the production of a hyperosmotic solution in the upper part of the intestine. This causes a rapid transfer of fluid from the vascular compartment into the intestine. This results in intestinal distension and an abrupt fall in circulating volume which, in subjects intolerant of such a fall, gives rise to systemic symptoms.

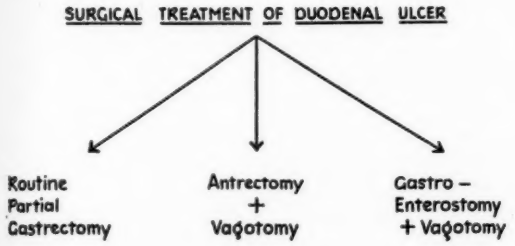

FIGURE I.
Surgical treatment of duodenal ulcer.

No doubt this theory is correct in some patients, and the use of insulin or tolbutamide would provide a practical solution by minimizing the effects of the osmotic disturbance in the gut wall. However, there are other patients in whom other complex factors must operate. In some, psychological factors seem to play the dominant role.

Malabsorption After Gastrectomy.

Work on the malabsorption syndrome, such as that outlined by Professor Kay of Sheffield (1960), may provide the answer to our major problem—the patient who fails to gain weight after gastrectomy. In some of these patients recent work suggests that small-gut obstruction of some degree occurs, and this leads to a change in the bacterial flora of the gut with consequent changes in the mucosal pattern and its ability to perform its absorptive functions to a normal degree.

Modern broad-spectrum antibiotics can provide great benefit as a temporary measure, but surgical relief of the obstruction is usually indicated.

Hæmatemesis without Obvious Cause.

I am sure that no surgeon enjoys the prospect of empirical partial gastrectomy for severe gastro-duodenal hæmorrhage. However, from time to time we are faced with this problem, and there is now little doubt that partial gastrectomy should be performed in the majority of cases.

Fortunately, in most of these patients our blind operation stops the bleeding. No doubt in many of these patients we have removed some small acute erosion. From my experience I am inclined to think that in most of the male bleeders alcohol has been the causative factor, usually in association with the irritable stomach of the emotionally unstable subject. In women, it is usually possible to exclude alcohol as an irritant, but in many of them there has been recent emotional stress which sometimes has been treated by A.P.C. powders or some similar remedy.

In view of the recent report of Manning and O'Connor (1960) on the conservative treatment of bleeding peptic ulcers, I suppose that we must become even more circumspect before resorting to surgery, but I am sure that there will always remain this problem group of bleeding stomachs for which surgery seems to be the only answer.

When we resort to surgery, it is important not to overlook the cause of the bleeding, especially in those cases in which double pathology may exist.

In those very worrying cases in which bleeding recurs, then I feel that we must be guided by that great

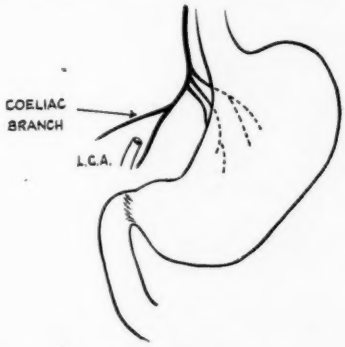

FIGURE II.
In selective vagotomy the cœliac branch of the posterior vagus, in particular, is preserved.

gastrectomist, Norman Tanner (1959), who advises a quasi-total, rather than total gastrectomy, leaving only one or two centimetres of cuff of stomach. The functional result is much the same as a total resection, but the operative mortality is less, and it usually does not require thoracotomy.

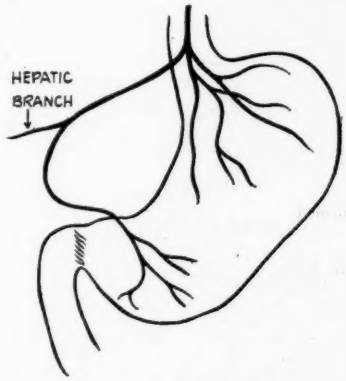

FIGURE III.
Distribution of the anterior vagus.

Gastric Polyps and their Problems.

Gastric polyps are uncommon, but when present, provide many problems. We must always respect the radiological diagnosis of gastric polyp because it has obvious pitfalls. Clinically it is practically impossible to make the diagnosis of gastric polyp(s), and so we are largely dependent upon the radiological finding, and to a lesser degree, upon gastroscopy.

If we take note of a recent survey of 465 patients from the Mayo Clinic by Huppler and his colleagues (1960), we are impressed by the difficulties involved. Operations were performed on 300 of these patients. The surgical pathological findings revealed that 60% of the 300 patients had benign gastric polyps, 20% had other types of benign lesions and 20% had malignant lesions. It was decided

that X-ray examination is the most accurate diagnostic procedure, but it is less accurate in the case of gastric polyp(s) than in the case of most gastric lesions.

In my own experience, I have found gastric polyps a most difficult clinical problem, especially in management. There is no doubt that the majority must be explored, and this exploration includes wide gastrotomy and adequate inspection of the mucosa. In some cases we have double pathology, as in the following case.

A female patient, aged 68 years, presented in July, 1959, complaining of recurrent episodes of pain in the upper part of the abdomen. She claimed that the pain usually occurred after eating, but could occur at any time. Flatulence was sometimes marked. The pain was

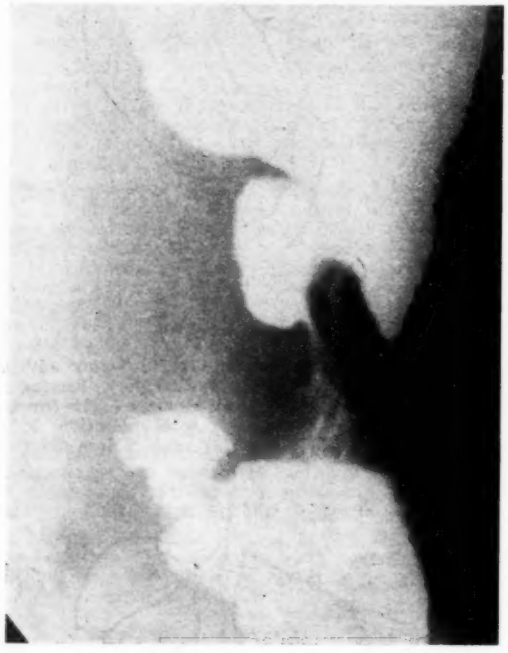

FIGURE IV.
Barium-meal X-ray study showing a large benign lesser-curve gastric ulcer.

not relieved by antacids. She had suffered from a severe melæna in 1958, requiring blood transfusion. There was no significant finding on physical examination. The barium-meal X-ray examination showed a duodenal diverticulum and a prepyloric polyp. Laparotomy confirmed these radiological findings (Figure VI). The pathologist reported that the wall of the duodenal diverticulum showed inflammation and the gastric polyp was benign. The patient has remained symptom free.

As a general rule, if the polyp is single and apparently benign, simple local excision should be performed and frozen-section examination carried out. If there is no sign of malignancy, nothing further need be done other than strict observation in the future. Should the frozen section reveal malignant changes, then conservative partial gastrectomy seems the best treatment.

Even in the event of multiple polyps extending to the cardia, total gastrectomy is rarely indicated as the long-term survival is surprisingly high. Frequently, fulguration or local excision of the remaining polyps through the open end of the stomach can be performed.

Hypertrophic Gastritis.

This condition is now well recognized, but often we find that the clinical and radiological diagnosis is incorrect. We must always be on guard lest the diagnosis of this disease cloaks the existence of an underlying gastric carcinoma. If one is in any doubt, operation must be carried out, as it provides the highest degree of accuracy in diagnosis.

However, in some few cases I have found that it can pose real problems in management, such as are illustrated by the following case.

A female, aged 59 years, presented in January, 1960 complaining of epigastric pain and vomiting of "coffee grounds". She had originally undergone a partial gastrectomy in 1954 for her original symptoms, which she claimed were very like those from which she suffered at present. Her surgeon at the time told her that she had a small duodenal ulcer. At various intervals during the past

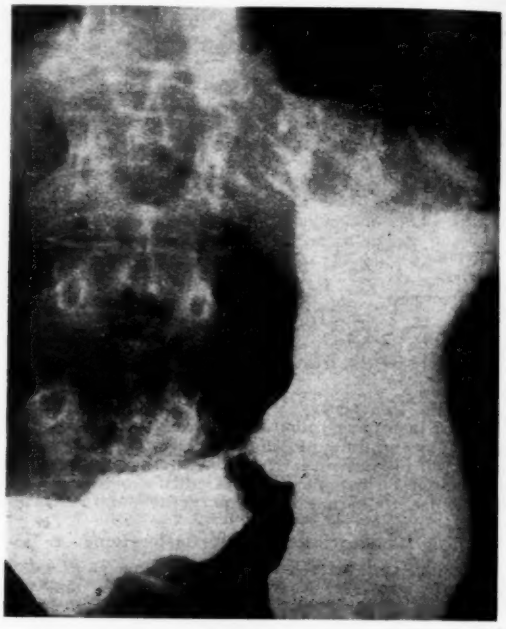

FIGURE V.
Barium-meal X-ray study showing malignant hour-glass contracture of stomach due to gastric ulcer treated medically for more than two years.

six years she had undergone further partial gastrectomy, vagotomy and cholecystectomy, in an attempt to relieve her pain. Her weight had dropped from 14 stone to six stone since the original operation. Examination revealed the Belsen type of physique one sometimes sees after partial gastrectomy. There were no relevant abdominal findings. Barium-meal X-ray studies showed hypertrophic gastritis of the gastric remnant. Œsophagoscopy was normal. In view of her cachexia and past history, it appeared that any operative treatment would be unlikely to give any benefit. Medical measures have been used with moderate success.

In such cases it would seem that one is obliged to perform total gastrectomy if bleeding continues, but what an unpleasant prospect.

Provided that we can exclude gastric carcinoma and polyposis, then in the majority of cases we should persevere with conservative treatment. Hypertrophic gastritis has little or no cancer potential, and is thus primarily a medical problem in which considerable relief can be obtained.

Problems in Pyloric Obstruction.

Pylorospasm.

From my observations, pylorospasm is a very common problem and is one of our modern stress syndromes. It

is frequently found in association with other spasmodic disorders, such as are found in the region of the ampulla of Vater. I have been so impressed by this association that it is my current practice to perform pyloroplasty plus sphincterotomy in cases of ampullary spasm when

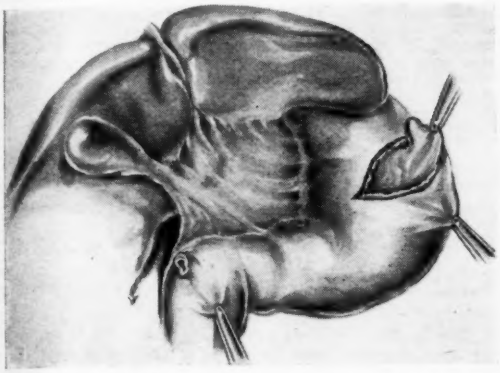

FIGURE VI.

Operative drawing showing first and second parts of duodenum retracted medially. The base of the duodenal diverticulum and pre-pyloric polyp are demonstrated.

operation excludes mechanical obstruction at the ampulla. In my short series to date, I have been favourably impressed with the results of this empirical procedure.

Pylorospasm can be seen to extreme degrees and may well give the impression that some organic lesion is present (Figure VII). A skilled radiologist can usually differentiate pure spasm from organic obstruction. Carstairs *et alii* (1958) have continued to remind us that headache, particularly of the migrainous type, is often associated with delayed gastric emptying. The physiological mechanism is not quite clear.

The mistake of performing operation on these patients is sometimes followed by a trail of unfortunate sequelæ such as adhesive small-gut obstruction and, of course, continued abdominal pain. If it is remembered that attacks of vomiting without abdominal pain are rarely due to abdominal disease, and that the association of headache with nausea and vomiting is most frequently due to migraine, such mistakes should be avoided.

We should not hesitate to repeat the barium-meal X-ray examination in any doubtful cases. Perhaps we might also change the radiologist.

However, it must not be forgotten that patients may suffer from both migraine and peptic ulceration.

Pyloric Stenosis and Maintenance of Nutrition.

No doubt all of us have seen patients with apparently severe pyloric stenosis maintain their general nutrition to a remarkable degree. It would seem that, like so many things in nature, physiological adaptation can occur. The stomach mucosa, it would seem, can perform absorptive functions to some degree under such circumstances. The following case illustrates the clinical problem.

A professional man, aged 46 years, was seen on June 26, 1957 with severe pain in the right hypochondrium which appeared to be due to an attack of acute cholecystitis. He claimed to suffer from recurrent epigastric discomfort and flatulence, not especially related to meals. During this acute episode of pain he was treated in hospital on conservative measures, with relief of symptoms. He refused further investigation as "he was too busy". He again presented in February, 1960 with further pain in the same region, and on this occasion consented to X-ray examination. The cholecystogram showed that the "Telepaque" was held up in the stomach for some reason, and as a result no gall-bladder shadow was shown. The barium-meal study revealed definite pyloric stenosis, which was most likely due to a chronic duodenal ulcer. The patient refused any operative treatment, as he had not lost weight or felt otherwise distressed. Since then he has remained in a surprisingly good state of nutrition and has continued to enjoy a full life.

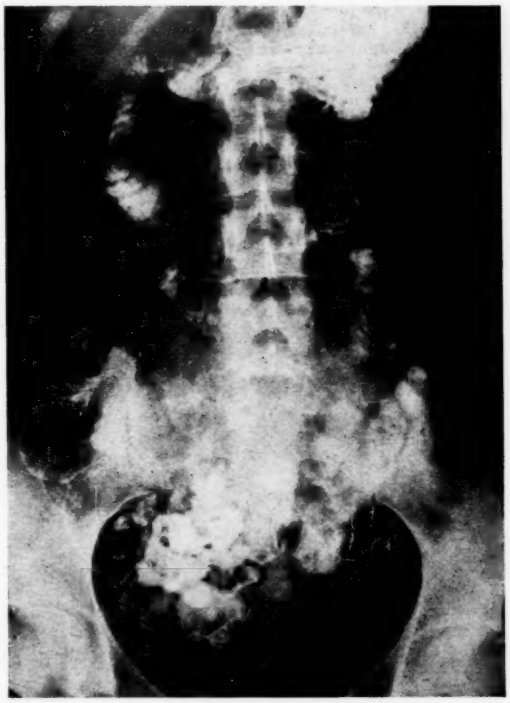

FIGURE VII.

Barium-meal X-ray study showing eight-hour gastric residue in a case of pylorospasm. The barium-meal study performed a fortnight later was completely normal. This patient was a very nervous young woman.

Thus I think that there are some cases of pyloric stenosis where conservative treatment can be justified, especially if we can exclude neoplastic obstruction. In

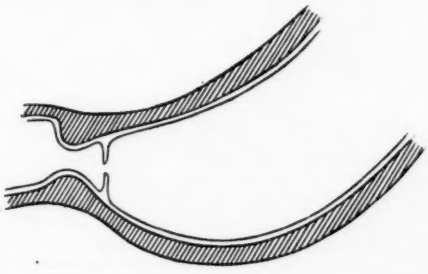

FIGURE VIII.

This shows the pre-pyloric site of the mucosal diaphragm in the case discussed.

some cases, spasm is certainly an aggravating cause. The case selected for illustration also demonstrates the wisdom of barium-meal examination, especially if there is gastric retention of the dye during oral cholecystography, as this may reveal a lesion of the stomach and duodenum.

Mucosal Diaphragm Simulating Pyloric Stenosis.

Mucosal diaphragm is an obscure condition only recently described, and can cause considerable confusion. This obstruction is due to a mucosal diaphragm either proximal to or at the level of the pylorus, with no visible or palpable cause on external examination of the stomach. The diaphragm consists of a double layer of mucous membrane, with a small aperture usually central in position (Figure VIII). It is really only possible to demonstrate a mucosal diaphragm in the fresh, unopened gastric specimen. The following case report illustrates this interesting condition.

A housewife, aged 35 years, presented in September, 1959 with a history of having suffered from indigestion during the previous five years, with progressive increase in severity. There was no definite relation to food. A barium-meal X-ray examination performed five years previously was said to reveal no abnormality, but one performed the previous year showed some "pyloric deformity" (Figure IX). She had undergone intensive medical treatment for ulcer by a skilled physician, without relief.

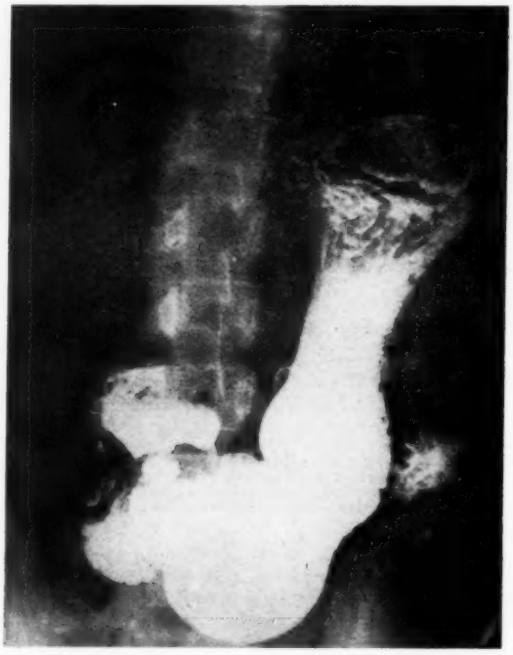

FIGURE IX.

The barium-meal X-ray study shows a pre-pyloric constriction, which proved to be a mucosal diaphragm.

Examination revealed a well-nourished, rather nervous woman who had no significant physical findings. Laparotomy was ultimately performed on October 2, 1959 and macroscopically the stomach and duodenum appeared normal. I decided to divide the pylorus for further inspection and, to my surprise, found that a diaphragm was present just proximal to the pylorus. After division of both the diaphragm and pylorus nothing abnormal could be seen on the mucosal surface. A limited Billroth I partial gastrectomy was performed. The patient made an uneventful recovery and has remained well. The pathologist could find no evidence of chronic ulceration at the site of the diaphragm.

Idiopathic Pyloric Hypertrophy in an Adult.

Idiopathic pyloric hypertrophy has always been an intriguing condition, not only in the various theories of ætiology, but also because of the radiological errors which exist.

A male patient, aged 51 years, presented in June, 1960 with a six-year history of recurrent epigastric pain lasting about 10 minutes, unrelated to meals. His appetite was always good and his weight had remained constant. He claimed that his mother and two sisters had died of "cancer of the stomach", and therefore he naturally had a fear of cancer. Examination showed a well-nourished nervous man who appeared to have a gastric succussion splash. The barium-meal X-ray study showed a pyloric antral deformity, which the radiologist thought might be due to cancer. Laparotomy in July revealed a pyloric antral tumour about two inches long, and as it was difficult to be sure that this was not a carcinoma, partial gastrectomy was performed. The opened specimen showed considerable pyloric muscular hypertrophy extending about two inches proximally, and about half an inch in thickness (Figure X). The pathologist reported that this was due to a true hyperplasia of the muscle coat.

In such a case, with a strong family history of gastric cancer, the X-ray diagnosis should be given serious consideration, but perhaps on more careful study by the radiologist, the error could have been avoided.

At operation, palpation of the stomach suggested carcinoma, and thus partial gastrectomy appeared the correct treatment.

In this patient there were many factors in his life which could have caused repeated pylorospasm, and, as we know, some suggest that continued pylorospasm may lead to hypertrophy.

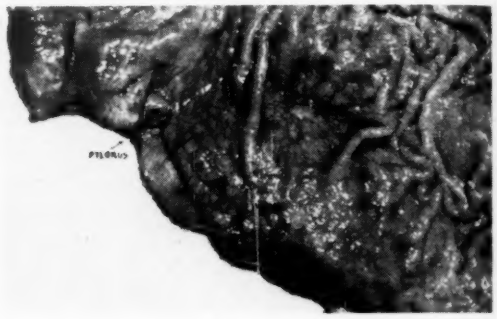

FIGURE X.

The pyloric antral muscular hypertrophy is illustrated.

Obstruction due to Food Bolus after Partial Gastrectomy.

I have had the experience of operating upon three patients for small-gut obstruction due to impacted food bolus, on whom previous partial gastrectomy had been performed. In such patients it is quite obvious that they have not chewed their food properly, and in the absence of a pyloric sphincter, the bolus of food may impact completely or may cause bouts of subacute obstruction. I feel that bouts of subacute obstruction have not been sufficiently recognized in the past as a cause of pain after gastrectomy.

Thus we must emphasize to our patients after gastrectomy not only to eat "little and often", but also to chew well, stressing that this can only be done with adequate teeth. Some patients dislike wearing false teeth and in such people, ordinary food simply cannot be chewed properly. I have recently had occasion to remove two separate impacted boluses of steak-and-kidney pie in a patient who rarely bothered to use his false teeth.

Early Diagnosis of Gastric Cancer.

Gastric cancer remains a challenge, not only in its treatment, but perhaps more so in its early diagnosis. All of us make errors in the diagnosis of this neoplasm, but we must not accept our ineptitude in diagnosis as inevitable. One great lesson that I have learned over

the years is to take considerable notice of the patient's opinion. If he thinks that he might have a cancer of the stomach, sometimes he is correct, despite lack of clinical symptoms (Figure XI). Another lesson to be remembered is to be careful in the prescribing of tonics for patients in the cancer age group. A surprising number of run-down patients harbour a gastric cancer.

Gastric cancer patients may not lose weight for a considerable time, despite hepatic secondaries. Sometimes the presenting symptoms in the abdomen are due to the hepatic secondaries and not to the primary tumour. We must not be misled by non-contributory X-ray studies. Clinical acumen is sometimes far more important.

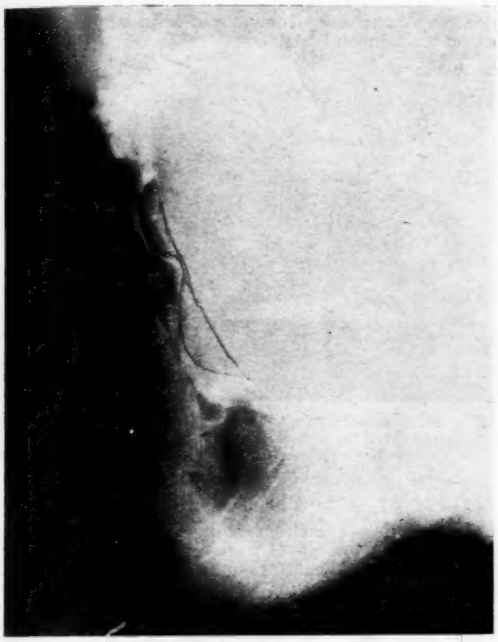

FIGURE XI.

Barium-meal X-ray study showing outline of lesser-curve gastric ulcer, which was discovered during routine examination, and which proved to be an inoperable carcinoma.

What can be done to achieve earlier diagnosis? I would suggest a greater all-round awareness of the disease, improved methods of cytological study and the use of the newer agents such as "Gastrografin" for X-ray investigation. Perhaps the recent work on the serum of cancer patients may ultimately provide some practical assistance.

In Brisbane we have little experience of exfoliative cytology, especially in gastric study. Recent work suggests that this form of investigation is becoming increasingly valuable, but only when performed by those skilled in its usage.

Gastric cytology should not be used as a routine, but it can be a most useful adjunct to radiology and gastroscopy. Various methods of collecting specimens are under investigation. I am rather interested in the retractable nylon brush, as recommended by Nieburgs (1959) of New York. In a recent personal communication he claims to have become more accurate than suggested in his published article.

It is only by being prepared to listen to new suggestions that our diagnostic armamentarium will be enlarged to enable us to locate more readily one of the most silent of our surgical foes.

Sarcoma of the Stomach.

Every surgeon delights in finding something unusual and rare, and gastric tumours occasionally provide some measure of excitement. Sarcoma of the stomach in its various forms sometimes presents as an unusual problem.

I will now give some details of a recent case which illustrates some of the problems involved.

A housewife, aged 67 years, presented in March, 1960 complaining that she had felt a lump in the left side of her abdomen during the past three months. She had no other symptoms. Examination revealed a healthy-looking patient with a firm, mobile abdominal lump in the left iliac fossa, which could be pushed into the left pelvis and felt on vaginal examination in the left fornix. This tumour was naturally considered to be ovarian in nature. Laparotomy revealed a circumscribed, firm, irregular, fleshy-looking tumour about four inches in diameter, arising from the lower part of the greater curvature of the stomach. The tumour was resected (Figure XII). There were many palpable tumours in the liver, which were considered to be secondaries. The pathologist considered the tumour to be an unusual type of gastric sarcoma which was difficult to classify exactly, but resembled a fibrosarcoma in many respects. The tumour appeared to have little invasive tendency and had not involved the mucosal surface of the stomach. The patient has remained well since the operation, and there has been no evidence of weight loss or other signs of deterioration.

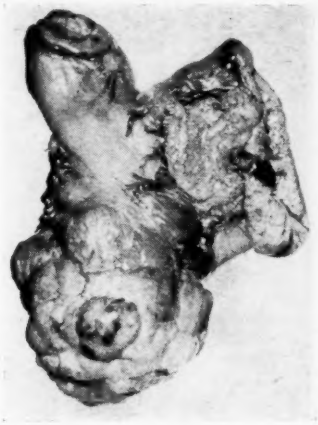

FIGURE XII.

Resected specimen of stomach showing large sarcoma arising from greater curvature.

We must observe the odd way in which some of these tumours present. We should also note that these tumours are usually easily resectable at operation. In most cases operation is well worth while, despite the presence of secondaries, because even then long-term survival can occur, in contradistinction to carcinoma. There is also likely to be some difficulty in exact histological diagnosis, but, of course, this may be of purely academic importance.

Various writers have reported series of extraordinary long-term survival. It is emphasized that the diagnosis of sarcoma of the stomach is most difficult, and nothing exists to differentiate it clinically from carcinoma. (X-ray examination and laboratory investigations are not of great assistance.)

It is suggested that when one sees a young person with a large, palpable mass in the epigastrium, who appears less emaciated than one would expect with carcinoma of equal size, a lymphosarcoma of the stomach should be given serious consideration.

The prognosis for lymphoid tumours is almost twice as good as the best five-year survival figures for carcinoma, and the prognosis for patients with leiomyosarcoma is even better.

Radiological Traps.

I think we must accept the fact that in a certain proportion of cases these mistakes cannot be avoided, and only careful laparotomy will reveal the true diagnosis. The old adage "All that glitters is not gold" is worth remembering, even in clinical study.

There are two traps of which I have become particularly wary, namely, the following.

Filling Defects of the Stomach.

Filling defects of the stomach are often labelled as carcinoma when, in fact, they can be anything from a normal exaggeration of gastric rugæ to pressure from an extragastric organ such as the spleen.

I would like to draw attention to the excessively mobile spleen as a cause of extragastric pressure, as I have found that it can produce a considerable gastric filling defect on barium-meal study.

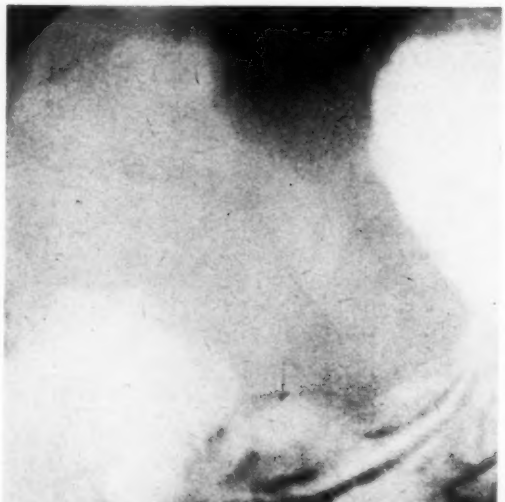

FIGURE XIII.
Barium-meal X-ray study showing pseudo-ulcer.

The Apparent Ulcer.

If we feel that the barium-meal X-ray picture of an ulcer is not consistent with the patient's clinical behaviour, then we must always doubt the X-ray diagnosis. Sometimes only full laparotomy will reveal the truth, as in the following case.

A young man, aged 29 years, presented in February, 1959 with a two-year history of recurrent melæna and attacks of abdominal pain, unrelated to meals. He had undergone laparotomy many years previously, owing to some abdominal injury which nearly caused death. It appeared from Army hospital records that the peritoneal cavity contained large quantities of blood, but, owing to the poor state of the patient's condition, further exploration was not carried out. The patient recovered after a stormy convalescence.

The barium-meal X-ray examination performed at the Mater Hospital in February, 1959 showed a "lesser curve gastric ulcer" (Figure XIII). Laparotomy in February, 1959 revealed that the radiological appearance of ulcer arose from dense adhesions holding the lesser curvature to the liver, due, no doubt, to the previous intraabdominal injury. The real cause of the melæna was found to be a solitary carcinoid tumour of the terminal part of the ileum causing intussusception. The tumour was resected (Figure XIV), and since then the patient has remained completely symptom free.

What a tragedy it would have been if one had continued to treat such a patient conservatively, and thus have missed the opportunity for cure of a serious tumour.

This is only one of the many instances in which we must not place undue reliance on any one ancillary aid to diagnosis. Clinical judgement is still the best weapon in our armamentarium, and a carefully performed laparotomy remains our most powerful ally in the diagnosis of the difficult abdomen.

FIGURE XIV.
The resected specimen of terminal part of the ileum showing solitary carcinoid as a cause of melæna.

Summary.

I have reviewed current problems in gastric surgery from a personal point of view. There is still a great deal to be learnt about the stomach, and clinical problems abound.

We seem to be nearing a solution for the problem of the surgical treatment of the duodenal ulcer, but perhaps before that final solution is reached, the physicians will have found another way to outwit us, and snatch a further operation from our grasp.

Surgeons are still worried by the patient who suffers from hæmatemesis without obvious cause, and a complete solution has not yet been found.

The physiology and pathology of the pylorus remain a source of clinical interest.

The challenge of the early diagnosis of gastric cancer still confronts us all, whether we be general practitioners or specialists. Methods of cytological study have yet to be developed to full advantage, at least in Brisbane.

Obstruction due to food bolus after gastrectomy is perhaps more common than we realize.

Radiological traps abound, and we must not forget our basic principles in clinical diagnosis.

In all these problems, clinical teamwork is essential. The gastro-enterological unit should be regarded as an essential section of any large hospital. It is only by full cooperation with our medical and radiological colleagues that surgeons can hope to solve the many problems in gastric surgery which still exist.

Acknowledgements.

I would like to thank Sister Mary Patrice of the Mater Hospital and the University Photographic Department for their photographic services.

To Miss M. Waugh, librarian, and Miss L. Pegus, medical artist, of the Queensland University Medical

School, I express my thanks for their services willingly rendered.

References.

BRUCE, J., CARD, W. I., MARKS, I. N., and SIRCUS, W. (1959), "The Rationale of Selective Surgery in the Treatment of Duodenal Ulcer", *J. roy. Coll. Surg. Edinb.*, 4: 85.

BURGE, H. W. (1960), "Vagal Nerve Section in Chronic Duodenal Ulceration", *Ann. roy. Coll. Surg. Engl.*, 26: 231.

CARSTAIRS, L. S. (1958), "Headache and Gastric Emptying Time", *Proc. roy. Soc. Med.*, 51: 790.

HUPPLER, E. G., PRIESTLY, J. T., MORLOCK, C. G., and GAGE, R. P. (1960), "Diagnosis and Results of Treatment in Gastric Polyps", *Surg. Gynec. Obstet.*, 110: 309.

KAY, A. W. (1960), "Some Surgical Aspects of the Malabsorption Syndrome", *Brit. med. J.*, 1: 1291.

LE QUESNE, L. P., HOBSLEY, M., and HAND, B. H. (1960), "The Dumping Syndrome. I: Factors Responsible for the Symptoms", *Brit. med. J.*, 1: 141.

MANNING, W. K., and O'CONNOR, K. (1960), "A Report on 500 Cases of Bleeding Peptic Ulcer Treated Medically with Minimal Transfusion of Blood", MED. J. AUST., 1: 918.

NIEBURGS, H. E. (1959), "Tubeless Gastric Analysis and Cytologic Procedures", *Surg. Clin. N. Amer.*, 39: 1213.

NIEBURGS, H. E. (1960), personal communication.

STRANGE, S. L. (1959), "Giant Innocent Gastric Ulcer: Its Behaviour and Treatment", *Brit. med. J.*, 1: 476.

TANNER, N. C. (1959), in "Recent Advances in Surgery", Fifth Edition, Churchill, London: 332.

TANNER, N. C. (1960), personal communication.

TREATMENT OF GASTRIC CANCER.

By J. GRAYTON BROWN, M.S., F.R.C.S., F.R.A.C.S.,

From the Royal Melbourne Hospital, Melbourne.

IT is the duty of surgeons treating cancer to review their experiences and to report to their colleagues from time to time. The task of reviewing the treatment of carcinoma of the stomach, although rather sobering, is relieved by some gratifying results.

Surgery should be directed towards cure by a radical operation but the extent of the growth and its metastases may allow a palliative procedure only.

Frozen section is always advisable for immediate diagnosis. The type of tumour will influence the type of operation. On one occasion in this series, what appeared to be a carcinoma macroscopically proved to be diagnosed microscopically as a sarcoma; the patient benefited by post-operative deep X-ray therapy. An ulceration over a leiomyoma may resemble that of a malignant tumour.

Palliative Procedures.

The objects of palliation are to relieve unpleasant symptoms, to improve the patient's well-being and to prolong life.

Gastro-enterostomy for primary tumours obstructing the pylorus in the presence of metastases is rarely worth while, owing to the impaired gastric emptying in these patients; partial gastrectomy is much more satisfactory. Occasionally gastro-enterostomy is the only possible procedure when a large, irremovable primary tumour obstructs the pylorus.

Even in the presence of metastases, partial gastrectomy may be worth while as a palliative procedure to remove the primary tumour which is causing distressing symptoms. The condition of these patients may be greatly improved by the removal of the primary tumour.

Palliative total gastrectomy may occasionally be indicated when there is complete obstruction at the cardio-œsophageal junction.

Radical Surgery.

In radical excision for attempted cure, the surgical principles are wide excision of the primary tumour and radical excision of the regional lymph glands. These principles are limited by what is compatible with life, and, equally important, by what is compatible with a comfortable existence.

If the line of section is reasonably clear of the primary tumour, there is sufficient evidence with regard to decreased morbidity and mortality to indicate that subtotal gastrectomy is the operation of choice. However, Pack *et alii* (1947) recommend the principle of total gastrecomy for all such cases, but still carry out subtotal gastrectomy on many occasions. McNeer *et alii* (1956) found that after subtotal gastrectomy 50% of recurrences were in the stomach remnant, but other metastases were also found at the same time.

The lymph field should be excised radically by ligation of the left gastric, the right gastric and the right gastro-epiploic vessels at their origins, and by the removal of the spleen. The greater omentum is removed to the level of the transverse colon to give maximum clearance of the regional lymph field.

A decision whether to perform total or subtotal gastrectomy can be made only at the time of operation, and with this in view an upper oblique incision should first be made. This will be sufficient for subtotal gastrectomy and it can be easily extended if a thoraco-abdominal approach is found to be necessary.

Tumours limited to the pyloric antrum and not associated with macroscopic metastases will be suitable for a subtotal gastrectomy.

The anastomosis may be completed by the Billroth I or the Billroth II (Pólya) method. It is of interest to recall that Billroth carried out the former operation in 1881 for stomach cancer. Total gastrectomy will be required when there is insufficient margin of unaffected tissue between the primary tumour and the œsophagus, or when there is local infiltration of the pancreas, liver or transverse colon. A "leather bottle" stomach also requires a total gastrectomy. A thoraco-abdominal incision is, in my opinion, essential for adequate excision and anastomosis in these cases. Anastomosis is usually carried out by means of a Roux-en-Y jejunal anastomosis, although occasionally œsophago-duodenostomy is preferable if a speedy operation is indicated and the duodenum is mobile.

More radical excision of the primary tumour and lymph fields has become the standard procedure since improved methods of anæsthesia, resuscitation and prophylactic chest treatment have been introduced.

This extended resection has been accompanied by an improvement in operative mortality and the five-year survival rate. Thus the results of a series of 270 cases from the Royal Melbourne Hospital disclosed that only 70 patients had had a radical operation for attempted cure. The follow-up was satisfactory in 63 cases, and of these 12 (19%) patients survived for five years. Eleven (17%) had died soon after operation and the remaining 42 had died within five years. In this limited series there was no significant difference in the five-year survival rates between patients who had total and those who had subtotal gastrectomy procedures. One of the most impressive series reported by other surgeons is that of Welch and Wilkins (1958); they claim that 46·7% of their stomach cancer patients who had no metastases and who were suitable for subtotal gastrectomy survived five years. Usually about 30% appears to be worthy of reporting (Trapeznikov, 1959; Berkson *et alii*, 1952).

From these figures we cannot expect any great improvement from surgical excision alone. Radiotherapy is of minimal value in carcinoma and would appear to offer no future claim.

Chemotherapy.

I firmly believe that chemotherapy as an adjuvant to surgical removal holds the greatest hope for prolonging survival or for cure. With this in mind, and knowing that cancer cells circulate in the portal circulation in increased numbers after surgery, Warren Cole (personal communication) began four years ago to give injections

of nitrogen mustard into the portal circulation at the time of operation. Similarly Trapeznikov (1959) gave "Sarcolysin" (Perevodchikova and Blokhin, 1958). Recently I have been using thio-TEPA, injecting 15 mg. into the portal vein and 15 mg. into the peritoneal cavity at the time of operation, and giving three daily injections of 15 mg. after operation. Daily white-cell counts have not shown any pronounced depression. These doses are relatively small and it may be safe to increase the dosage. Regional portal perfusion would be an advantage until less toxic substances are developed, as I am confident they will be.

It is my belief that surgical excision with the administration of improved cytotoxic agents will be the pattern of future control or cure of gastric cancer.

Today appropriate radical surgery combined with the most effective chemotherapeutic agent available is the treatment which should be adopted and carefully assessed by every surgeon who is anxious to advance our knowledge of this serious condition.

Summary.

1. Although the results of surgical treatment of carcinoma of the stomach are poor, the outlook is not hopeless.

2. Palliative procedures are worth while and the different operations are discussed.

3. Indications for the various types of radical surgery are given. There is a place for either total gastrectomy or subtotal gastrectomy.

4. The results of 270 cases of gastric cancer are analysed.

5. The use of combined surgical and chemotherapeutic treatment for gastric cancer is advocated.

References.

BERKSON, J., WALTERS, W., GRAY, H. K., and PRIESTLEY, J. T. (1952), "Mortality and Survival in Cancer of the Stomach, Colon and a Statistical Summary of the Experience of the Mayo Clinic", *Proc. Mayo Clinic*, 27: 137.

MCNEER, G., LAWRENCE, W., ORTEGA, L. G., and SUNDERLAND, D. A. (1956), "Early Results of Extended Total Gastrectomy for Cancer", *Cancer*, 9: 1153.

PACK, G. T., MCNEER, G., and BOOHER, R. J. (1947), "Principles Governing Total Gastrectomy—A Report of 41 Cases", *Arch. Surg. (Chicago)*, 55: 457.

PEREVODCHIKOVA, N. I., and BLOKHIN, N. N. (1958), in "Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity", Churchill, London: 110.

TRAPEZNIKOV, N. N. (1959), "Results of Surgical Treatment of Cancer of the Stomach", *Brit. med. J.*, 2: 857.

WELCH, C. E., and WILKINS, E. W. (1958), "Carcinoma of the Stomach", *Ann. Surg.*, 148: 666.

GLUTEN-FREE DIETS IN AUSTRALIA.

By THEO COOKE, M.B., B.S.,
Curramulka, South Australia.

THE necessity of gluten-free diets for children with cœliac disease has been recognized over the last eight to 10 years, opinion at present being that the intake of gluten should be completely eliminated and that a premature return to a gluten-containing diet is highly undesirable (Frazer, 1960).

Some workers now think that the cœliac factor is the glutamin-containing peptides of the alcohol-soluble gliadin fraction of gluten, which, owing to enzymatic dysfunction, pass unchanged through the intestinal mucosa (Fanconi, 1959; Fleck, 1960).

An admirable summary of the current thought regarding gluten enteropathy has been written by Frazer (1960), who stated:

> Present information indicates that the deleterious agent is a relatively low molecular weight, heat-stable, ultrafiltrable substance (or substances); resistant to peptic/tryptic digestion, but destroyed by enzymes present in pig intestinal mucosa, or by a deamidase, such as papain. It occurs in wheat gluten and appears to be transported readily with the gliadin fraction. There is some evidence that it is not included in the phospholipid fraction. It is closely associated with and may be a peptide (or peptides).

Frazer also stated that there are grounds for considering that the effect of wheat gluten in gluten-induced enteropathy is that of directly inducing intestinal dilatation and hypomotility, which are among the first signs to return (they are detected radiographically) when gluten is reintroduced into the diet; and he summed up the evidence for wheat gluten being either a truly allergic agent, or alternatively, a pharmacologically toxic agent which may work by inhibiting the production of acetylcholine. He quoted evidence which suggests there is a genetic background in some patients.

In practice the cœliac factor is found mainly in wheat and rye flours. Continental patients, it seems, are affected also by oat gliadin (Fanconi, 1959), although most Australian and British cœliac children seem to tolerate oatmeal satisfactorily. However, the question of oats should perhaps be borne in mind in unresponding patients, and its effect is easily tested.

Fletcher and McCririck (1958) point out that in Great Britain the exclusion of gluten-containing wheat flour (and with it, such useful items as sausages, pies, fritz and fried fish in batter) from the diet of children reduces the intake of protein, calcium, iron, thiamine, nicotinic acid and riboflavine to points well below recommended levels. In adult diets the average intake of protein is reduced below normal, and the average intake of the other nutrients to very near the recommended minimal levels.

Fanconi (1959) believes that the wasting and hypotonicity of the abdominal musculature is accentuated by riboflavine deficiency, and also advises supplements of vitamins D, A and K. In addition, Shaw (1960) has elaborated the occurrence of hypoprothrombinæmia and bleeding in sprue.

The thiamine content of the Australian diet, even with a normal intake of wheat flour, is notoriously low. In my own small practice, the results of thiamine excretion tests performed during 1958 and 1959 on 13 selected patients who were apparently normal but complained of fatigue are given. The tests were performed by the Institute of Medical and Veterinary Science in Adelaide. The excretion should exceed 100 μg. per day, while results between 100 and 150 μg. per day are considered sub-optimal. Eight patients had thiamine excretion test results of less than 100 μg. per day. The individual figures were 9, 25, 25, 55, 74, 83, 88 and 94 μg. per day respectively. Three patients had slightly better results, namely 110, 121 and 136 μg. per day. One patient gave a result of 195 μg. per day and one, who has been taking 30 mg. of thiamine daily for two weeks, topped the list with 220 μg.

It is plain therefore that although a gluten-free diet is the mainstay in the treatment of cœliac disease and sprue, attention must be paid to vitamin deficiencies, to iron and calcium deficiencies and occasionally to lack of folic acid or vitamin B_{12}. The diet may need to be enriched with a high content of gluten-free protein (for example, fresh or powdered milk, such as "Complan" or "Nesmida") to achieve a satisfactory weight gain. In addition, antidiarrhœal medication may be necessary in the initial stages, and prednisone may be needed during crises. In cases of severe weight loss, anabolic hormones may be used.

Frazer (1960) mentions that the following conditions should be considered in the differential diagnosis: pancreatic enzyme deficiency (this may be single or multiple, and may occur apart from fibrocystic disease); bile salt deficiency; intestinal infestation (*Monilia*, *Giardia* and *Strongyloides*); jejunal diverticulosis (localized or generalized); and a condition comprising jejunal and ileal lymphatic stasis, of unknown ætiology, which causes protein leakage and loss into the intestinal lumen, and is diagnosed by the recovery from the stools of labelled

polyvinylpyrrolidine, which has been administered parenterally. Other conditions are megacolon combined with malnutrition and chronic pancreatitis.

Caution should be exercised in diagnosing a gluten-induced enteropathy merely because the patient responds to a therapeutic trial of a gluten-free diet. Many dietary adjustments are involved, and the patient's improvement may be due to the fact that he is eating better-quality food, and not to the omission of gluten. Cases of unintentional and even voluntary malnutrition for socio-economic reasons are not unknown.

The emphasis in gluten-free diets up till now has been naturally placed on baby foods, and similar diets for older children and adults suffering from gluten-induced enteropathies are comparatively restricted, monotonous and unpleasant to follow. Fletcher and McCririck (1958), in an attempt to broaden such diets, wrote to a number of food manufacturers, and as a result published a list of gluten-free packaged foods available in Great Britain. This list was sufficiently large and varied to make such diets hardly any burden to the patient.

I had assumed that foods which were gluten-free in Great Britain would also be gluten-free when made by the same companies in Australia, and therefore allowed two adult patients with sprue to follow this list. When they failed to improve, I wrote to various Australian food manufacturers asking for information about their gluten-free products. The accompanying lists are the result, and give the most comprehensive details of gluten-free foods in Australia that I have been able to find.

It should be noted that some food lines which are gluten-free in Great Britain do contain gluten when made in Australia. Confectionery and sweets are mostly made with Australian liquid glucose, which is processed from wheat and may contain small amounts of gluten, and flour is frequently added. Jelly beans contain large amounts of wheat starch.

The first list is modified from Fletcher and McCririck, (1958), and contains foods which are forbidden in a gluten-free diet. As a general rule, all foods prepared or processed in any way must be assumed to contain gluten unless it is known otherwise.

These foods are: "Aktavite" (0·3-0·6% gluten); "All Bran"; baking powders; baby cereals[1]; baked or canned beans[1]; "Benger's Food"; biscuits; blancmange powder; "Bonox"; "Bournvita"; bread; breadcrumbs; buns; breakfast cereals[1]; cake and pudding mixes; cakes; cake decorations; canned meats[1]; caramels[1]; celery salt[1]; cheese spreads[1]; chocolate[1]; chocolate (drinking)[1]; chocolate and coffee spreads; Christmas pudding; chutney[1]; coffee essences[1]; confectionery and sweets[1]; cornflour[1]; cream (artificial); "Crispbread"; curry powder[1]; custard powder[1]; dessert powders[1]; "Farola"; "Farinoca"; fish canned in sauce; fish pastes; *glacé* fruits; gravy makers and browning[1]; groats[1]; "Horlicks"; horseradish sauce; ice cream (commercial); ice cream cones and wafers; ice cream powder[1]; infant and invalid foods[1]; instant desserts[1]; jelly beans; junket tablets[1]; lemonade powder; lemon cheese; lemon/orange curd; lemon pie filling[1]; luncheon meats; macaroni cheese; macaroni product; malt; malted milk drink; "Marmite"; "Marshmallow Creme"; marzipan; mayonnaise[1]; meat paste; meat (canned)[1]; meringues[1]; mincemeat[1]; mustard; noodles; oatmeal[1]; "Ovaltine"; "Oxo"; pastry; peanut butter; pepper[1]; pies; pickles; porridge oats[1]; potato crisps[1]; potato salad[1]; "Procera"; "Proferin" rolls; "Prolac"; puddings (canned); puffed wheat; rusks; "Ryvita"; salad dressings[1]; sandwich spreads and pastes[1]; sardines in sauce; sauces[1]; sausages; semolina; soups (canned)[1]; soup powder[1]; spaghetti; spices[1]; spreads[1]; stuffings; tomatoes in sauce; tomato juice[1]; trifle; vegetable salad[1]; vegetables canned in sauce; vermicelli; "Vita Weat"; "Weet Bix".

The following Cadbury-Fry-Pascall lines contain gluten: "Nut Lunch" chocolate; "Energy" chocolate; "Old Jamaica" chocolate; "Grilled Almond" chocolate; "Nougat Nut Roll"; "Milk Bar"; "Kookas"; butterscotch; "Shortcake" biscuits; "Sweetmeal" biscuits; "Bournvita". "Anchor" brand cream of tartar flour contains large quantities of gluten.

The following list, also modified from Fletcher and McCririck (1958) contains foods which are permitted in a gluten-free diet. Such foods are: almonds; bacon; beer; sodium bicarbonate; boiled sweets (clear only); butter; calves' foot jelly; capers; carraway seeds; cheese; chicory; cloves; cocoa; coconut; coffee (fresh or instant); colourings; "Complan"; cooking fat and oil; cream (dairy or tinned); cream of tartar; dried fruits; essences; fish (fresh or frozen); fish (canned in brine, oil or water); fruit (fresh or frozen); fruit juices and squashes; fruit tinned in syrup; gelatin; ginger; glucose; herbs; honey; jam and jam setters; jelly crystals; junket, rennet; lard; lemon juice; lemonade (bottled) and aerated waters; lentils; lime juice; margarines (cooking—some table margarines may contain gluten); marmalade; meat (fresh or frozen); milk (fresh, tinned or dried); olives; peels; prunes; raisins; rice; sago; salt; suet; sugar; sultanas; tapioca; tea; treacles; "Vegemite"; vegetables (fresh or frozen); vegetables (canned in brine or water); vinegar; wines and spirits; baker's yeast.

There are several cooking flours which are permitted, and these include (i) gluten-free wheat starch; (ii) cornflour[2]; (iii) soya bean flour; (iv) arrowroot. Of these, the most convenient flours for baking are cornflour and gluten-free wheat starch. The absence of gluten lessens the holding quality of the flour and necessitates slightly longer cooking times, but with a little practice good results may be obtained. Soya bean flour and arrowroot produce poor results, except perhaps in skilled hands.

A gluten-free baking powder may be made according to the following recipe (from the "Uncle Toby" Home Service):

6 oz. gluten-free cornflour
7 oz. bicarbonate of soda
4 oz. cream of tartar
4 oz. tartaric acid

Mix all ingredients and rub through a hair sieve. Repeat twice, then store in an airtight tin.

Recipes for gluten-free biscuits, cakes and puddings may be obtained from Parsons Pty. Ltd. (Melbourne and Sydney) and from the "Uncle Toby" Home Service (Sydney).

Gluten-free, home-made bread may be baked from various recipes, but will last two or three days only. Proprietary meringue breads are a little expensive, but will last two weeks or more if deep-frozen, and are baked by (i) Invalid Food Products Ltd. (Melbourne) and (ii) Golden Crust Bakery (Adelaide)—beginning June, 1960.

Recently a new chemical leavening agent—glucono-delta-lactone (made by and available from the Pfizer Corporation, or, in South Australia, from the Adelaide Children's Hospital Store)—has made it possible to bake successfully home-made bread of normal taste and texture. It may also be used for leavening cakes and buns, and further descriptions of its use therein are given by Feldberg (1959), and Townsend and Rowe (1960). The following bread recipe (Townsend and Rowe, 1960) has been kindly supplied by Dr. E. S. Sims. It takes a total time of about 45 minutes to prepare and bake. (A commercial "Pre-Mix" preparation of this recipe has recently (March, 1961) been made available from Sanitarium Health Food shops.)

1¼ oz. baker's yeast preferably (or else fine, pregelatinized starch—Amylo Products, Port Adelaide)
10 oz. water (cold)
6 oz. fresh milk

[1] Some brands of these foods are gluten free and are those given in a later list.

[2] "Brown and Polson's" and Parsons' "Globe" brands of cornflour are completely gluten free. I have been informed that the gluten contents of "Nurses" and "Kream" brands of cornflour have been reduced, in the last year or two, to 0·1-0·3%, but they should not be used when completely gluten-free cornflours are available.

15 oz. gluten-free flour (specifically, wheat starch with a nitrogen assay of less than 0·075%; this wheat starch gives much better results than other gluten-free flours)
6 oz. skimmed milk powder.
1 oz. glucono-delta-lactone
½ oz. bicarbonate of soda
¼ oz. salt

Place yeast or "Pre-gel Starch" into small "Mixmaster" bowl, pour in fresh milk and water and beat thoroughly. Scrape down sides of bowl when necessary and continue beating (speed 5) until mixture is smooth. This process takes approximately five minutes. Pour into a large bowl and set up in mixer.

Mix together glucono-delta-lactone and bicarbonate of soda, sieve together with skimmed milk powder and cornflour. Add these dry ingredients with salt gradually to liquid mixture while beating (speed 5). Mixers may slow down during additions of dry ingredients, but speeds up as batter becomes clear and smooth. Scrape down when necessary.

Scale immediately into one-pound, well-greased bread tins, smooth top with a wet spoon. Allow five minutes' recovery and bake at 452° F. for 25 to 30 minutes.

If, at the mixing stage, the batter climbs the beaters, switch off, scrape down and paste up with a spatula, then continue to mix.

* The mixer referred to is a "Sunbeam Mixmaster". A planetary type may be more effective.

The following manufacturers have assured me (July and August, 1960) that their products as listed below are gluten-free. Only these firms have been approached, and it is likely that others would be equally cooperative if asked.

Anchor Products Ltd. named the following: apricots (dried); cinnamon; cloves (whole); coconut (all types); castor sugar; coffee (essences, pure ground and with chicory); cordial extracts; culinary colours; currants; curry powder; lemon essences (pure and imitation); vanilla essence; "Snowflake" brands ice cream mix and flavourings, icing sugar (one- and two-pound packs only) and plastic icing; "Anchor" jellies; mixed fruit; nutmeg; Parisian essence; peas (blue, green and split); lemon peel; mixed peel; pepper (white and black); pimento (whole); tomato sauce; seeded raisins; soups (chicken noodle, pea, and mixture); Spanish cream; mixed spices.

W. Angliss and Co. supplied the following names: 12 oz. taper "Hamper" corned beef; 12 oz. rounds of "Imperial" trim, lamb tongues, sheep tongues, calf tongues, pork lunch tongues.

Berri Cooperative Packing Union named these products: juices—orange, grapefruit, tomato, tomato *purée*, apricot nectar, peach nectar, grape juice (light and dark); dried fruits—apricots, pears, peaches, nectarines, figs, currants, sultanas and seeded raisins.

Brookers (Aust.) Ltd. named canned fruits, jams and fruit juices only.

Cadbury-Fry-Pascall Pty. Ltd. supplied these names: chocolate blocks—"Dairy Milk", "Candy Nut", "Honey Crisp", "Fruit and Nut" (dark); "Caramello", "Brazil Nut", "Nut Milk", "Scorched Almond", "Almond and Raisin", "Lemon", "Dairy Milk Rolls", "Peppermint Rolls", "Fry's Chocolate Cream", "Cub Bars", "Bears"; chocolate bar lines—6d. "Dairy Milk Flake"; chocolate assortments—"Milk Tray", "Selected", "Roses", "Peppermint Chocolate Creams", "Scorched Almonds"; Pascall lines—"White Heather Chocolates and Candies", "Treasure Toffees", "Cream Caramels", "Liquorice Rolls", "Fruit Bonbons", "Fruit Drops", "Fruit Salad", "Jellies", "Jubes", 9d. "Fruities", 1s. 4d. "Sky High Toffees", 1s. 6d. barley sugar, "Scotch Mints"; food drinks—"Bournville" cocoa, drinking chocolate.

Cottees Ltd. named all their products except "Lemon Spread" and "Caramel Milk Bar Syrup".

Gordon Edgell and Sons Ltd. listed vegetables—asparagus (tips, spears and cuts), beans, beetroot, carrots, cauliflower, mixed vegetables, peas, sauerkraut, tomatoes (whole or *purée*) and mushrooms (whole and sliced); juices—orange and tomato; fruits—apples, peaches, pears and berries; soups—tomato and oyster; savoury rice. A number of Edgell-Gerber baby foods are gluten free. These may be found listed on pages 19, 20 and 21 of the Edgell-Gerber booklet "Foods for Baby".

D. and J. Fowler Ltd. named "Lion" vanilla custard powder; "Lion" instant puddings; "Lion" jelly crystals; citrus peel; coffee essence; cordial extracts.

Glaxo-Allenbury's (Aust.) Pty. Ltd. named "Complan"; "Farex" rice cereal; "Osterina" Number 1 and Number 2.

H. J. Heinz Company Pty. Ltd. suggested "New England Style" baked beans in sugar-cured ham sauce; baked beans in tomato sauce vegetarian; vegetable salad in mayonnaise; mayonnaise; savoury cucumber slices; green peas; tomato sauce; tomato ketchup; tomato juice. A number of Heinz baby foods are gluten free. These are marked on the Heinz chart of "Average Nutritive Values", which may be obtained through the local grocer.

Kellogg (Aust.) Pty. Ltd. named "Corn Fakes"; "Sugar Frosted Flakes"; "Rice Bubbles"; "Corn Flake Crumbs".

Kraft Foods Ltd. named all their cheese products (both natural and processed carton and jar lines); "Vegemite"; Kraft ice cream mix.

Clifford Love and Company Ltd. named "Brown and Polson's Cornflour"; "Uncle Toby" custard powder; "Uncle Toby's Quick Dessert".

Nestlé Company (Aust.) Ltd. named "Sunshine" full-cream powder; "Ideal" unsweetened milk; sterilized reduced cream; "Vi-Lactogen"; "Lactogen"; "Nescafe"; plain dark and milk chocolates; "Nesmida"; "Arobon". Also named "Nestogen" malted milk, "Milo", "Maltogen", "Ricory" and "Maggi" soups, all of which contain some gluten which has been altered by the process of malting or hydrolysis; these processes reduce the gluten into its constituent amino acids and other substances. The Nestlé Company state that they believe that malted or hydrolysed gluten (gliadin) will not cause any reaction, and mention confirming reports by Dutch investigators dating back to 1955 (Fleck, 1960). This presumably refers to the work of Van de Kamer and Weijers (1955), and is substantiated by Frazer (1960). However, I gave "Maggi" soup cubes (supplied by courtesy of the Nestlé Company) to one patient with gluten intolerance, and the soup cubes twice caused a smart exacerbation of her diarrhœa. Perhaps this group should be permitted only with caution.

Parsons Pty. Ltd. named cornflour; custard powder; rice flour; ground rice; arrowroot; "Cornina"; "John Bull" rolled oats; "One-Minute" oats.

Tom Piper Ltd. products were: meats—lamb tongues and corned beef; fruits—mixed dried fruits, mixed candied peel and fruit mince spread; cordials—"Milk Bar" syrups (all except caramel).

Rosella Preserving and Manufacturing Company products were tomato sauce; fruit chutney; Worcester sauce; soups—tomato, asparagus, pea and mushroom; tomato juice; canned tomatoes; canned fruits; jams; jellies; sweet corn; asparagus spears; sliced beetroot; stringless beans green peas; tomato paste.

Sanitarium Health Food Company products included soya bean flour; soya bean compound (for making soya bean milk); gluten-free bread "Pre-Mix".

Simpson Bros. Ltd. had no gluten-free products.

White Wings Pty. Ltd. supplied "White Wings" instant pudding; "Dewdrop" jellies; "Noddy" ice block mix.

World Brands Pty. Ltd. supplied copha; "Mellah" cooked desserts—vanilla, chocolate and caramel; lemon pie dessert filling; instant puddings—vanilla, chocolate, caramel, raspberry, pineapple and banana; "Vidale" table and cooking margarines.

It should be pointed out that many of the above foods (particularly custard powders, desserts and sauces) are regarded as being commercially gluten free—that is, they may have a gluten content of about 0·1% measured in terms of nitrogen assay. In order to reach an intake of

10 grammes of gluten a day—the amount given by Frazer (1960) for up to 21 days in order to provoke a cœliac exacerbation—it would be necessary to eat about 500 serves a day of instant dessert with a gluten content of 0·1%. Therefore it is probable that most patients with gluten-induced enteropathies could eat the foods listed above. Suffice it to say that those who cannot will have to stay on a more restricted diet.

Summary

Gluten-free diets are reviewed briefly, with the emphasis on the need to watch carefully the intake of protein, calcium and vitamins. Lists are published of permitted and forbidden foods, and also of a moderate variety of Australian proprietary prepared foods, in an effort to make such diets more varied and less burdensome for older children and adults.

Acknowledgements.

I wish to acknowledge my indebtedness to the various firms mentioned, particularly the Nestlé Company (Aust.) Ltd. and D. and J. Fowler Ltd., for their willing cooperation; to Dr. A. Kerr Grant, who advised me to check the gluten content of Australian prepared foods; and to Dr. E. B. Sims, who read the manuscript, for his assistance, advice and encouragement.

Reference.

FANCONI, G. (1959), *Annales Nestlé*, Number 4: 3.

FELDBERG, C. (1959), "The Use of Glucono-Delta-Lactone in Bakery Products", *Bakers' Digest.*

FLECK, M. C. (1960), personal communication.

FLETCHER, R. F., and MCCRIRICK, M. Y. (1958), "Gluten-Free Diet", *Brit. med. J.*, 2: 299.

FRAZER, A. C. (1960), "Medical Progress: Cœliac Syndrome", *J. Pediat.*, 57: 262.

SHAW, S. (1960), "Idiopathic Steatorrhœa and Hæmorrhage Due to Malabsorption of Vitamin K", *Brit. med. J.*, 2: 647.

TOWNSEND, F., and ROWE, A. (1960), "Gluten-Free Bread for Cœliacs", *Commonwealth Department of Health, Food and Nutrition Notes and Reviews*, 17: 67.

VAN DE KAMER, J. H., and WEIJERS, H. A. (1955), "Cœliac Disease. V. Some Experiments on the Cause of the Harmful Effect of Wheat Gliadin", *Acta pædiat. (Uppsala)*, 44: 465.

SERUM GLUTAMIC OXALOACETIC TRANSAMINASE (S.G.O.T.) IN THE DIAGNOSIS AND PROGNOSIS OF MYOCARDIAL INFARCTION.

By R. W. BEAL, M.B., B.S.,

Fellow in Medicine, Clinical Research Unit,[1] *Royal Prince Alfred Hospital, Sydney*

WITHIN the past decade estimations of the activity of various body enzyme systems have been added to the diagnostic armamentarium of the physician, and to a lesser extent, the surgeon. The estimations which have found the greatest acceptance have been those of the serum glutamic oxaloacetic transaminase (S.G.O.T.) and the serum glutamic pyruvic transaminase (S.G.P.T.), which have their chief application in diseases of the heart and liver. The results are not regarded as diagnostic in their own right, but more as aids to diagnosis and prognosis and, when taken in conjunction with other clinical and biochemical data, they have been proved to be of considerable value.

The results of serum glutamic oxaloacetic transaminase (S.G.O.T.) estimations in 47 patients who were known to have, or who were suspected of having, a recent myocardial infarction are presented in this paper and discussed.

[1] Supported in part by the National Health and Medical Research Council of Australia.

Method.

Several different methods have been reported for the estimation of S.G.O.T. activity. La Due *et alii* (1954) described a photometric method, and were associated with Karmen (1955), who used a method which employs quantitative paper chromatography. Other photometric methods of varying degrees of difficulty have since been described (Cabaud *et alii*, 1956; Reitman and Frankel, 1957).

The method used in this investigation to estimate S.G.O.T. activity was that of Reitman and Frankel (1957) with certain modifications. The estimation depends on the catalytic action of the specific transaminase in the system shown in Figure I.

The standard solutions were modified in the manner suggested by Holden and Weiden (1958).

The sample to be tested was usually received as 5 ml. of clotted blood in a sterile bottle, from which the serum was removed after being centrifuged within two hours of collection. During this study it was found that no alteration could be demonstrated in S.G.O.T. activity if the blood were allowed to stand without separation for periods of up to 24 hours. During this investigation it was again shown that no change resulted in the transaminase activity of the serum if it was kept refrigerated for two to three days, or if it was deep-frozen (that is, at 0-4° C.) for an indefinite period of time (Karmen *et alii*, 1955).

For the estimation, 0·2 ml. of serum is added to a tube containing 1 ml. of the aspartate substrate, standing in a water bath at 37° C. Exactly one hour after the serum has been added, 1 ml. of 2,4 dinitrophenylhydrazine (2,4 DNPH) is added with gentle agitation. The tubes are now allowed to stand at room temperature. Twenty minutes after the addition of the 2,4 DNPH, which halts the reaction, 10 ml of 0·4 N sodium hydroxide is run in; this brings up the characteristic colour, the optical density of which is read exactly 30 minutes later, at 505μ, with water used as the blank. In this investigation the readings were done on a Beckman quartz spectrophotometer, model DU. The results are read directly from a calibration curve constructed at the outset of the investigation, and checked at regular intervals during it (Sigma Company modification of the method of Reitman and Frankel).

With each set of estimations blanks were run, and duplicate estimations were done in some instances.

Material.

The method for S.G.O.T. determination was set up in the course of an investigation into the value of this enzyme system estimation in liver disease (Beal, 1959), and the S.G.O.T. estimations in this group of cardiac patients were performed partly as a diagnostic service.

The majority of the patients came from the Professorial Medical Unit of the Royal Prince Alfred Hospital. There was a relatively large number of patients in this series in whom the diagnosis of myocardial infarction was doubtful, since there were many patients with obvious myocardial infarcts who did not have S.G.O.T. estimations. There was as well a number initially suspected of having a myocardial infarction, whose electrocardiograms were normal. The test was also requested for a number of patients in whom a myocardial infarction was considered in the differential diagnosis, but not seriously entertained as a diagnosis. These patients have been included in the series. They were usually patients who gave a history of vague chest pain, or who evidenced cardiac arrhythmias of uncertain origin.

Wherever possible serum was taken within 12 hours of the onset of chest pain, in an attempt to achieve a base-line reading before the S.G.O.T. levels rose, since most workers report the maximum S.G.O.T. concentration occurring between 10 and 30 hours from the commencement of the infarction, with a return to pre-infarctive levels within three to seven days. In general, when only one estimation has been done, the serum has been collected betwen 12 and 36 hours of the onset of the pain. In some cases it was difficult to assess from the history the precise time of the commencement of the coronary arterial occlusion, so the time of commencement of chest

pain, or in some cases, the time at which a sudden increase in the severity of chest pain occurred, is taken as zero time.

The group of controls selected for the establishment of a normal range of S.G.O.T. activity were either normal, healthy adults, or adult out-patients suffering from diseases not affecting the heart, liver and musculature, and in which the S.G.O.T. is known not to be elevated (Wróblewski, 1958, 1959).

Results.

The group of normal controls, as delineated above, had S.G.O.T. values which ranged from 2 to 22 units, with a mean of 12 units. Fifty-six readings were done in 52 patients. When reporting the results, the range of normality was accepted as 5 to 30 units.

Forty-seven patients had S.G.O.T. estimations performed in an attempt to confirm or exclude the presence of myocardial infarction. Of these, 22 (47%) did not have elevated S.G.O.T. readings, and in eight of these cases serial readings were done. The range of values was from five to 26 units, with a mean value of 15 units, which differs very little from the normal values for both the mean and the range. None of these patients showed evidence of myocardial infarction on their electrocardiograms, either at the time of the normal S.G.O.T. reading, or at a later stage in the illness.

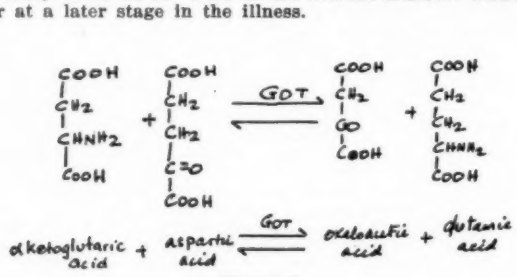

FIGURE I.

Chemical reaction used as basis for S.G.O.T. estimations in present series.

There were 25 patients who had elevated S.G.O.T. levels. The range was from 43 units to 134 units, with a mean of 72 units. This range is somewhat lower than those in some reported series (Burstein and Harjanne, 1959; Bruce *et alii*, 1958; Dewar *et alii*, 1958), but here the range of normality is lower as well, and the lowest reading obtained in a proven myocardial infarction (43 units) is twice the accepted upper limit of normal for this series; this conforms to the pattern described by other authors, who state that the S.G.O.T. elevation in myocardial infarction is from two to 20 times the normal value (La Due and Wróblewski, 1954, 1955; Agress *et alii*, 1955). The distribution of abnormal readings is set out in Figure II.

Of these 25 patients, 14 had electrocardiographic evidence confirming their infarction prior to or simultaneous with the S.G.O.T. estimation. Three had dubious electrocardiograms, which did not materially contribute to the diagnosis at the time of the S.G.O.T. reading. With the other eight patients, the diagnosis rested largely with the transaminase estimation, either because of previous electrocardiographic changes which remained unaltered (six cases), or because of the absence of any changes in the electrocardiogram at a time when the S.G.O.T. level was already elevated (two cases).

Of the eight patients who had already had abnormal electrocardiograms, six had previous infarcts with no evidence of further electrocardiographic change and two had cardiac arrhythmias which prevented the diagnosis of infarct being made with any certainty.

All patients who had electrocardiographic evidence of myocardial infarction showed a considerable rise in their S.G.O.T. readings (that is, more than twice the upper limit of normal). There were three patients who had elevated S.G.O.T. values without any evidence of myocardial infarction at any time during the investigation. The implications of this observation are discussed below.

Discussion.

In the past five years several reports have appeared in the literature which have helped to establish the value of S.G.O.T. estimations in myocardial infarction, as well as in hepatic and neuro-muscular disorders. Wróblewski, who has played a leading rôle in the investigation of transaminases and other enzymes, has recently reviewed the present state of knowledge concerning these enzymes (Wróblewski, 1958, 1959).

Initially it was felt by some that the S.G.O.T. estimation was a relatively non-specific test, of comparable value to the C-reactive protein, the erythrocyte sedimentation rate changes and temperature rises associated with myocardial infarction. However, it has been shown conclusively that the rise in the S.G.O.T. level after myocardial infarction is a reliable indication of the presence

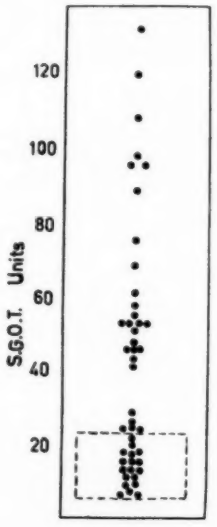

FIGURE II.

Distribution of maximum S.G.O.T. readings in the patients in this series. The broken-line rectangle indicates the normal range.

and extent of such an infarction. La Due and Wróblewski (1954) and Agress *et alii* (1955) showed in dogs, in whom they produced myocardial infarction by experimental occlusion of a coronary artery, that the extent of the cardiac muscle necrosis was proportional to the rise observed in S.G.O.T. levels. They also demonstrated that the S.G.O.T. levels did not rise when coronary artery occlusion was produced in dogs which led to ischaemic changes, but not to infarction. Clinical correlation has been described by Dewar *et alii* (1958), who were able to show a positive relationship between the height of the S.G.O.T. level and the severity of the myocardial infarct, as assessed by the electrocardiographic changes.

Burstein and Harjanne (1959) and La Due (1957) have shown that changes in S.G.O.T. levels in myocardial infarction are more reliable and consistent than the changes seen in the C-reactive protein. Dewar *et alii* also showed in their series of myocardial infarctions that the S.G.O.T. level rose 24 hours before the temperature rose, and up to a week before the erythrocyte sedimentation rate was altered.

The mechanism of S.G.O.T. elevation is still not known, but there is evidence to suggest that part, if not all, of the rise in S.G.O.T. activity which follows upon myocardial death and damage is due to the release of this enzyme (and others) into the circulation following either death of the individual cells, or the loss of integrity of the cellular membrane to a degree sufficient to allow the enzyme to pass through (Rudolph, 1955).

Elevated S.G.O.T. Levels in Proven Myocardial Infarction

In these patients, electrocardiographic evidence of myocardial infarction was already available when the S.G.O.T. readings were done. In cases in which serial estimations were available (14 cases), it was possible to form some estimate of the severity of the infarct. However, in some patients serial estimations were not possible, for a variety of reasons — for example, in that patient whose S.G.O.T. level was the lowest of those considered diagnostic, the blood was taken six hours after the onset of the chest pain, and only some minutes before he died from ventricular rupture through a large transmural infarct.

CASE I.—A case history typical of this group is that of a woman, aged 64 years, who was known to be hypertensive, and to have suffered from angina pectoris for years. She was admitted to hospital at 1 a.m. on February 9, 1960, after the onset two hours previously of acute, constricting chest pain, which radiated up into the neck and down the left arm. Her blood pressure on admission was 80/40 mm. of mercury. The pain was of sufficient severity to require two injections, each of one-sixth of a grain of morphine, within an hour for its relief. An electrocardiogram taken on admission to hospital showed ischæmic changes, but no evidence of myocardial infarction. Later that day, an infarct became obvious on a progress tracing, and on February 11, 1960 a pericardial friction rub was heard. Serial S.G.O.T. estimations were done, and the results are shown in Figure II.

FIGURE III.
A typical serial S.G.O.T. pattern in a patient with a relatively severe myocardial infarction (Case I).

Elevated S.G.O.T. with Previously Abnormal Electrocardiograms.

The S.G.O.T. determination assumes its greatest diagnostic value in a patient whose electrocardiogram shows evidence of previous infarction or an arrhythmia (Dewar *et alii*) and therefore makes the diagnosis of a fresh infarct difficult.

Reinfarction.—It is known that in reinfarction there is a secondary increase in the transaminase levels (Baron *et alii*). In the present series of patients there were a number in whom the S.G.O.T. level assumed greater importance, as these patients all gave histories which suggested recent myocardial infarction, but exhibited no change in their electrocardiograms, which were already abnormal as the result of previous infarcts. It was obviously of prime importance to know whether or not these patients had suffered reinfarction, as this consideration directly influences the further exhibition or continuation of anticoagulant therapy, and to a greater or less degree alters the prognosis. Eight patients in this series were known to have had previous electrocardiographically-proven myocardial infarcts. There were further equivocal changes in the electrocardiograms of two patients, and no change in those of the other six at the time of the diagnostic S.G.O.T. reading. In six cases there were significant S.G.O.T. level elevations diagnostic of reinfarction, with serial readings which gave further confirmation.

CASE II.—A man, aged 64 years, had been in hospital since June, 1959 with a proven myocardial infarct. He had been on anticoagulant therapy since his admission. At 9 a.m. on July 6, 1959 he experienced further crushing chest pain. An S.G.O.T. reading of 28 units was obtained four hours after the pain occurred, and a further reading taken 36 hours after the pain occurred was 48 units. He was regarded as having had a further small myocardial infarction, and heparin therapy was recommenced. After some days, electrocardiographic evidence of the reinfarction became apparent, although this was not evident at the time of the diagnostic S.G.O.T. reading.

Arrhythmias.—Estimations were performed on four patients with arrhythmias in this series, and two were considered to be diagnostic of myocardial infarction.

CASE III.—The patient was a man, aged 76 years, who was admitted to hospital in an attack of paroxysmal ventricular tachycardia. It was thought that a myocardial infarction might be the underlying cause of the tachycardia, but evidence from the electrocardiogram did not help. The estimated S.G.O.T. level 20 hours after the onset of the attack was 57 units. Later figures were within normal limits. He was treated with anticoagulant therapy and a number of drugs were used in an attempt to restore normal rhythm. He later died after several further attacks of paroxysmal ventricular tachycardia. Autopsy was not performed.

Elevated S.G.O.T. Without Electrocardiographic Changes.

In three cases in this series there was an increased S.G.O.T. level without evidence of myocardial infarction. All patients had levels which were well above the mean S.G.O.T. value for patients with myocardial infarction. (Their readings have not been included in the above group of elevated S.G.O.T. readings.)

CASE IV.—A woman, aged 70 years, was admitted to hospital with congestive cardiac failure and left bundle branch block. A silent infarct was suspected at this time. Her S.G.O.T. level shortly after admission was 500 units, and fell to a level of 58 units within a week, at which stage her congestive cardiac failure had been brought under control. She later became uræmic and died. No evidence of myocardial damage was found at autopsy, while the liver showed evidence of recent congestion.

There have been recent reports (Shields and Shannon, 1958; Bang *et alii*, 1959) of a number of patients who have had definite rises in S.G.O.T. levels with a history suggesting myocardial infarction but without electrocardiographic evidence. In most cases these rises were of the order of five to 10 times that expected in myocardial infarction. In practically all these cases, it was possible to demonstrate histological evidence of centrilobular necrosis which was thought to have resulted from acute hepatic congestion. Shields and Shannon also showed that in those patients with proven infarcts who had elevation of their S.G.O.T. levels outside the accepted upper limit for myocardial infarction, more than half had acute passive hepatic congestion which was felt to be the major contributing factor to the elevation of the S.G.O.T. level.

In each of the three cases in this present group, hepatic congestion was present at autopsy, and in the light of the work mentioned above, it was considered that the gross elevation of the S.G.O.T. level in the absence of myocardial infarction could be explained on the basis of post-congestive hepatic necrosis.

Prognostic Value of Elevated S.G.O.T. Levels.

As previously stated, a number of experimental studies (Agress *et alii*, 1955; Ruegsegger, 1959) and post-mortem observations have shown that the elevation of the S.G.O.T. level is proportional to the extent of the heart muscle damage occurring at the time of the coronary artery occlusion, providing that a reasonable number of readings are done within the appropriate time period. The prognostic value of an adequate series of S.G.O.T. readings over 48 hours after the onset of chest pain is considerable (Keele *et alii*, 1958), and by comparison with the mean values obtained in proven myocardial infarction, an estimate may be made regarding the extent of the infarction. For example, a comparison of the S.G.O.T. levels in Cases I and II is of interest. Although the latter patient had a second infarct, he made an uneventful recovery and left the hospital well. However, the former patient had evidence of shock for a longer period; she had persistent chest pain for a much longer period, and within three days she had developed evidence of pericarditis. The assessment of the severity of their infarcts by the respective levels of their S.G.O.T. is in accordance with the clinical assessment of the severity of their infarction.

Authorities differ in their statements on the time of maximal S.G.O.T. elevation after myocardial infarction. La Due and Wróblewski (1954) state that S.G.O.T. activity rises regularly within 12 to 24 hours, and returns to normal in three to six days after infarction, while Reitman and Frankel (1957) state that the 24 to 48 hour readings have close correlation with immediate mortality and the development of congestive cardiac failure. Bobek (1959) quotes their average maximum reading as occurring on the second day after infarction, while Baron states simply that the S.G.O.T. level is always raised in unequivocal acute myocardial infarction within 12 to 24 hours after infarction. Bruce *et alii* have suggested that a daily estimation be done for the first week.

Taking each of these statements into consideration, and also the experience gained in this investigation, a reasonable procedure would be to take the first blood sample as soon as the diagnosis is suspected — usually it is convenient to do this when the intravenous needle is in position prior to giving the initial dose of heparin. If the reading is made within 12 hours of the onset of the infarction, the value of this reading and subsequent ones is greatly enhanced. Then 5 ml. of blood can be withdrawn at eight to twelve-hour intervals (one can again utilize the intravenous needle prior to giving heparin), until an obvious rise and fall is obtained, or until it is certain that there has been no rise. This will prevent possible misinterpretation which may occur if a small, quick rise in the S.G.O.T. level is missed, should the level begin to fall at 16 hours, and it will also prevent a misleading interpretation of two normal readings at say four hours and 64 hours, which could well be the beginning and conclusion of a rise to a peak which occurred midway between the taking of the two readings. Wróblewski (1959) has recently reiterated that the maximum elevation might well be missed if serum sampling is not frequent enough during the first three days following infarction.

The variation in these different series also points to the conclusion that wherever S.G.O.T. estimations are done, reliance should be placed on local experience in the department where the estimations are being performed. It is thus the responsibility of each group to investigate a sufficient number of patients to acquire their own standards of normality, their ranges of abnormality, and the time relationships of the post-infarctive rise and fall of S.G.O.T. levels.

Summary.

1. A total of 47 patients have had S.G.O.T. estimations performed as an aid to diagnosis and prognosis of myocardial infarction. The levels were significantly elevated in all the 14 electrocardiographically proven infarcts in the series. Three patients who did not have myocardial infarction had grossly elevated S.G.O.T. levels, which were considered to be due to acute passive hepatic congestion.

2. Eight patients who had abnormal electrocardiograms due to previous infarction or cardiac arrhythmias were also investigated. Rises in S.G.O.T. levels considered to be diagnostic of mycordial infarction were found in six of them. Some of these later exhibited further changes in their electrocardiograms.

3. S.G.O.T. readings are of considerable value diagnostically in myocardial infarction, provided that the estimations are done early enough and often enough within the first two- to three-day period following infarction. The test is of prognostic value in the frank, electrocardiographically-proven myocardial infarction, because it gives an indication of the immediate and late prognostic problems, and emphasizes the therapeutic requirements. The S.G.O.T. level is of diagnostic value in patients whose electrocardiograms are already abnormal, and which may show no further alterations after myocardial infarction, as well as in some whose electrocardiograms show abnormality only some days after infarction.

4. A routine is outlined for the collection of an adequate number of specimens of serum at appropriate times after infarction.

Acknowledgements.

I wish to acknowledge with gratitude the helpful criticism of Professor C. R. B. Blackburn in the preparation of this paper, and the secretarial assistance of Miss B. James. I also wish to thank the honorary medical officers of this hospital, who requested these investigations on their patients.

References.

AGRESS, C. M., JACOBS, H. I., GLASSNER, H. F. LEDERER, M. A., CLARK, W. G., WRÓBLEWSKI, F., KARMEN, A., and LA DUE, J. S. (1955), "Serum Transaminase Levels in Experimental Myocardial Infarction", *Circulation*, 11: 711.

BANG, N. U., IVERSEN, K., JAGT, T., and TOBIASSEN, G. (1959), "Serum Glutamic Oxaloacetic Transaminase Activity as an Index of Centrilobular Liver Cell Necrosis in Cardiac and Circulatory Failure", *Acta med. scand.*, 164: 385.

BARON, D. N., ALEXANDER, C. P., BELL, J. C., and OAKLEY, C. M. (1958), "Serum Transaminase Estimation in the Investigation of Myocardial Infarction", *Quart. J. Med.*, 27: 533.

BEAL, R. W. (1959), Unpublished observations.

BOBEK, K., KARLICEK, V., and LAN, V. (1959), "Significance of Serum Transaminase in the Diagnosis and Prognosis of Cardiac Infarction", *Ter. Arkh.*, 31: 54, cited in *Abstr. Wld. Med.* (1959), 26: 93.

BRUCE, R., TODD, J. K., and LEDUNE, L. (1958), "Serum Transaminase: Its Clinical Use in Diagnosis and Prognosis", *Brit. med. J.*, 2: 1125.

BURSTEIN, J., and HARJANNE, A. (1959), "Glutamic Oxaloacetic Transaminase and C-reactive Protein in Myocardial Infarction", *Acta med. scand.*, 163: 175.

CABAUD, P., LEEPER, R., and WRÓBLEWSKI, F. (1956), "Colorimetric Measurement of Serum Glutamic-Oxaloacetic Transaminase", *Amer. J. clin. Path.*, 26: 1101.

DEWAR, H. A., ROWELL, N. R., and SMITH, A. J. (1958), "Serum glutamic Oxaloacetic Transaminase in Acute Myocardial Infarction", *Brit. med. J.*, 2: 1121.

HOLDEN, H. F., and WEIDEN, S. (1958), "The Preparation of Solutions for the Transaminase Test", MED. J. AUST., 2: 505.

KARMEN, A., WRÓBLEWSKI, F., and LA DUE, J. S. (1955), "Transaminase Activity in Human Blood", *J. clin. Invest.*, 34: 126.

KEELE, K. D., GOULDEN, G., and NEWMAN, M. J. D., (1958), "Prognostic and Diagnostic Value of Serum Glutamic Oxaloacetic Transaminase in Suspected Cardiac Infarction", *Lancet*, 2: 1187.

LA DUE, J. S., WRÓBLEWSKI, F., and KARMEN, A. (1954), "Serum Glutamic Oxaloacetic Transaminase Activity in Human Acute Transmural Myocardial Infarction", *Science*, 120: 497.

LA DUE, J. S., and WRÓBLEWSKI, F. (1955), "Significance of the Serum Glutamic Oxaloacetic Transaminase Activity Following Acute Myocardial Infarction", *Circulation*, 11: 877.

LA DUE, J. S. (1957), "Laboratory Aids in the Diagnosis of Myocardial Infarction", *J. Amer. med. Ass.*, 165: 1776.

REITMAN, S., and FRANKEL, S. (1957), "A Colorimetric Method for the Determination of Serum Glutamic Oxaloacetic and Glutamic Pyruvic Transaminases", *Amer. J. clin. Path.*, 28: 56.

RUDOSEGGER, P., NYDICK, I., FREIMAN, A., and LA DUE, J. S. (1959), "Serum Activity Patterns of Glutamic Oxaloacetic Transaminase, Glutamic Pyruvic Transaminase and Lactic Dehydrogenase Following Graded Myocardial Infarction in Dogs", *Circulat. Res.*, 7: 4.

RUDOLPH, L. A., DUTTON, R. E., jun., and SHAEFER, J. A. (1955), Glutamic-Oxaloacetic Transaminase Levels in Experimental Tissue Damage", *J. clin. Invest.*, 34: 1960.

SHIELDS, L. H., and SHANNON, R. E. (1958), "Acute Hepatic Congestion as a Factor in Elevated Serum Glutamic Oxaloacetic Transaminase Titres Above 400 Units", *Amer. J. med. Sci.*, 236: 433.

WRÓBLEWSKI, F. (1958), "The Clinical Significance of Alterations in Transaminase Activities of Serum and Other Body Fluids", *Advanc. clin. Chem.*, 1: 313.

WRÓBLEWSKI, F. (1959), "The Clinical Significance of Transaminase Activities of Serum", *Amer. J. Med.*, 27: 911.

SERUM PROTEIN VALUES IN NEW GUINEA HIGHLAND NATIVES.

By JEKABS KARIKS, M.D., D.T.M. & H.,
Department of Public Health, Port Moresby, Territory of Papua and New Guinea.

DURING the years 1958 and 1959 at Goroka in the Eastern Highland District of New Guinea, I had an opportunity to investigate the serum protein contents of 271 healthy village natives. The results of this investigation are presented in this paper.

Materials and Methods.

Blood samples were collected from apparently healthy adult native subjects living close to Goroka. Through a dry 18 gauge needle about 5 ml. of blood was withdrawn from an antecubital vein into a centrifuge tube. Total serum protein estimations were done immediately after the serum had separated from the clot. Serum samples which were not used immediately for electrophoresis were stored in an ordinary household refrigerator for several days.

The total serum protein estimation was carried out by the use of the copper sulphate specific gravity method as described by Phillips *et alii* (1950). The apparatus used for electrophoresis was that described by Flynn *et alii* (1951). Barbitone-boracic buffer was used as described by Budtz-Olsen (1958). For power supply, two coupled "A" batteries from an "A-B" radio battery set No. 482, yielding 90 volts, were used.

Three Whatman No. 1 filter paper strips 3 cm. wide were used at one time. These strips were suspended over a horizontal glass rod in a basin. Both ends of the strips were immersed in the buffer solution and the solution was permitted to soak through the strips. When they were soaked through, 20 c.mm. of serum were applied with a special applicator on the strips at the point where these crossed the glass rod. The power was connected after 20 or 30 minutes and the run was continued for 22 hours. This time was found to be the most suitable for clear separation of all five protein fractions.

The staining and washing method used was that described by Jencks *et alii* (1955). After staining, the paper strips were cut in segments 5 mm. wide according to the protein fractions as shown by staining. These segments were then put into centrifuge tubes each containing 4 ml. of 0·01N sodium hydroxide solution, and with occasional agitation were left there for 30 minutes. After this time the dye was eluted from the paper segments. The eluate was transferred to a Grey Wedge cuvette. The colour density in the eluate was read in a Grey Wedge photometer with the use of the green eyepiece. For the blank, clear 0·01N sodium hydroxide solution was used. On occasions when the colour density was too high for this instrument, two-fold to fourfold dilutions were made. During the whole investigation, one person only did the readings, using the electric bulb as the source of light.

Results.

The results of this survey are shown in Table I. Briefly summarized, it may be stated that, although the total serum protein contents in the New Guinea Highland natives were within normal limits, electrophoretically albumin and gamma-globulin fractions revealed a pattern similar to those observed in coloured people of tropical and subtropical countries by other investigators. However, individual values showed great variations, and in many New Guinea Highland natives similar protein values and patterns to those regarded as normal for white races were observed.

Discussion.

Differences in the serum protein contents as between adults in apparently healthy dark-skinned races inhabiting tropical and subtropical countries and those in a white population living in the same or temperate climatic areas have been reported by many investigators (Arens *et alii*, 1954; Arroyave *et alii*, 1960; Bakker *et alii*, 1957; Brading, 1958; Carr *et alii*, 1960; Curnow, 1957; Jansen, 1959; Holmes *et alii*, 1951; Stephens, 1948; Vera *et alii*, 1956; Wills *et alii*, 1951; Wilkinson *et alii*, 1958). In a previous paper (Kariks and Hipsley, 1961) it was possible to demonstrate that this difference in regard to increased gamma-globulin fraction was present at birth. To explain the observed differences in serum protein patterns between the dark-skinned and white races, several hypotheses have been advanced. However, it would lead us too far in unnecessary repetition to discuss again all the advanced arguments put forward for the support of these hyptheses. Suffice it to state only that each of these hypotheses has something to add to the final solution of the problem, but none so far has been satisfactory to explain the underlying physiological and physiopathological mechanisms which are the cause of these changes.

A great amount of clinical and experimental laboratory data is available on serum protein changes in health and diseases in temperate and in tropical climates. Löhr and Löhr (1922, cited by Marrack *et alii*, 1949), using T.A.B. vaccine, examined the changes in serum protein fractions in otherwise healthy subjects. After three spaced T.A.B. injections, the total serum protein conents in their subjects rose from 7·34 to 8·55 grammes per 100 ml. The albumin fraction decreased from 4·94 to 3·75 grammes per 100 ml., and the globulin fraction rose from 1·99 to 4·08 grammes per 100 ml. Changes occurred also in the fibrinogen fraction; it rose from 0·41 to 0·73 gramme per 100 ml.

Marrack *et alii* (1949), in their review on serum proteins, have listed the results of a number of investigators. Their conclusions were that as far as any generalization was possible, in acute infections the changes in the electrophoretic pattern were a reduction in the albumin content with a rise in the alpha-1 globulin fraction during the acute stage and a rise in the gamma-globulin fraction continued during the later stages and convalescence. In chronic infections, the changes were mainly a decrease of the albumin content, a rise in the gamma-globulin fraction and a very slight rise in the alpha-2 and beta globulin fractions.

Ogryzlo *et alii* (1959) also reported that in a number of acute and chronic clinical conditions caused by various pathogenic mechanisms, an increased globulin fraction and a decreased albumin content occurred in the serum.

Our Goroka serum protein results thus correspond with serum protein changes as observed in chronic infections; that is, the total serum protein values are within normal limits, the albumin content is decreased and the gamma-globulin fraction is increased. It may be of interest to mention here also that, by comparison, our mean values for Goroka male subjects closely resemble the mean values found typical of infectious hepatitis by Ogryzlo *et alii* (1959, Table I).

Observations made in the Goroka area show that, in general, the population there is comparatively healthy (Kariks *et alii*, 1960). However, the population at large suffers from some chronic or frequently recurrent infections and infestations. These infections and infestations are of high frequency, but of low intensity, and are seldom incapacitating in nature. The people attend to their daily routine in their village life and are classed as "healthy". In the Goroka area, diseases known to cause hyper-

TABLE I.

Mean Serum Protein Values (Grammes per 100 ml.) of Goroka Native Subjects; also Comparison with those of Healthy White Subjects and those found in Infectious Hepatitis.

Source.	Number of Subjects.	Total Protein. (Mean Content and S.D.)	Albumin. (Mean and and S.D.)	Globulins.			
				Alpha-1. (Mean and S.D.)	Alpha-2. (Mean and S.D.)	Beta. (Mean and S.D.)	Gamma. (Mean and S.D.)
Normal whites (Ogryzlo *et alii*, 1959)	—	7·22	4·32	0·32	0·62	0·80	1·15
Goroka females	131	7·30±0·63	3·52±0·47	0·24±0·06	0·58±0·08	0·89±0·13	2·06±0·37
Goroka males	140	7·41±0·61	3·62±0·48	0·29±0·05	0·64±0·13	0·99±0·16	1·87±0·33
Infectious hepatitis (Ogryzlo *et alii*, 1959)	—	7·44	3·69	0·35	0·66	0·92	1·80

proteinæmia, such as kala-azar, schistosomiasis, trypanosomiasis and filariasis, are not prevalent and malaria is only sporadic. This, then, explains why in this area the total serum protein contents are within normal limits and only the serum electrophoresis pattern is altered.

Convincing clinical and laboratory evidence is also now available that plasma cells are the site of gamma-globulin and antibody production (Bing, 1940*a* and *b*; Fleischhacker, 1940, 1941; Gormsen *et alii*, 1941; Fagraeus, 1948; Good, 1955; Bridges *et alii*, 1959; Nossal, 1959, 1960; Stobbe, 1960). Increased numbers of plasma cells have been demonstrated in the lymphatic tissues, the reticulo-endothelial system and the bone marrow in clinical conditions in which similar serum protein patterns are found to those described above (Bing *et alii*, 1937; Gormsen *et alii*, 1941; Taussig *et alii*, 1940). Good *et alii* (1950) have demonstrated even more critical association between the absolute numbers of plasma cells in the bone marrow and the gamma-globulin accumulation in the serum in rheumatic fever. Histological examination of sections of the tissues removed from chronically inflamed organs also reveal increased plasma-cell infiltration in these tissues. The presence of increased numbers of plasma cells whose function is antibody and gamma-globulin production will explain the increased gamma-globulin fraction in chronic inflammatory diseases.

A few of the factors which regulate the changes in serum albumin fraction in these conditions may be mentioned; increased catabolism during acute infection, liver-cell damage in chronic infection, the maintenance of normal osmotic pressure, and faulty dietary protein intake, absorption and utilization in different diseases may account for these changes.

Briefly summarized, this leads us to the following conclusion. In tropical countries, the native people are permanently or repeatedly exposed to acute or chronic infections and infestations, and this leads to increased numbers of plasma cells at the site of inflammation, in the reticulo-endothelial system and in the bone marrow. Increased numbers of plasma cells lead in turn to increased production of gamma globulin. To prove whether this is the mechanism and how exactly it functions, further and more detailed investigations are needed.

Summary.

The electrophoretic serum protein pattern of clinically healthy Goroka natives of the Eastern Highland District of New Guinea are described. The observation is made that this serum protein pattern closely resembles that frequently seen in chronic infections and infestations. A suggestion is made that this serum protein pattern is maintained by increased presence of plasma cells at the site of chronic inflammation, in the reticulo-endothelial system and in the bone marrow.

Acknowledgement.

I am grateful to the Director of the Department of Public Health of the Territory of Papua and New Guinea for permission to publish this paper.

References.

ARENS, L., and BROCK, J. F. (1954), "Some Aspects of Serum Protein Pattern of Africans", *S. Afr. J. clin. Sci.*, 5: 20.

ARROYAVE, G., SCRIMSHAW, N. S., PINEDA, O., and GUZMAN, M. (1960), "Electrophoretic Pattern of Hyperproteinæmic Sera in a Population Group of Rural Panama", *Amer. J. trop. Med.*, 9: 81.

BAKKER, A. W. I., BLIEK, A., and LUYKEN, R. (1957), "The Serum Proteins of Malaria Free Inhabitants of Central Netherlands New Guinea", *Documenta med. geograph. et trop.*, 9: 1.

BING, J., and PLUM, P. (1937), "Serum Proteins in Leucopenia. (Contribution on the Question about Place of Formation of Serum Proteins)", *Acta med. scand.*, 92: 415.

BING, J. (1940*a*), "Further Investigations on Hyperglobulinæmia. (Is Serum Globulin Formed from Plasma Cells and Reticulo-Endothelial Cells?)", *Acta med. scand.*, 103: 565.

BING, J. (1940*b*), "Investigation on Hyperglobulinæmia. (Occurrence and Degree of Hyperglobulinæmia in Various Diseases. Ratio between Hyperglobulinæmia. Formol-Gel Reaction)", *Acta med. scand.*, 103: 547.

BRADING, I. (1958), "The Serum Protein Pattern in Some Pacific Natives", MED. J. AUST., 2: 49.

BRIDGES, R. A., CONDIE, R. M., ZAK, S. J., and GOOD, R. A. (1959), "The Morphologic Basis of Antibody Formation—Development during the Neonatal Period", *J. Lab. clin. Med.*, 53: 331.

BUDTZ-OLSEN, O. E. (1958), "Haptoglobins and Hæmoglobins in Australian Aborigines, with Simple Method for the Estimation of Haptoglobins", MED. J. AUST., 2: 688.

CARR, W. R., and GELFAND, M. (1960), "The Biochemistry of the African in Southern Rhodesia. II. The Serum Proteins, Other Liver Function Tests, Blood Urea and Hæmoglobin of African Adults in Salisbury", *Trans. roy. Soc. trop. Med. Hyg.*, 54: 478.

CURNOW, D. H. (1957), "The Serum Proteins of Aborigines in the Warburton Range Area", MED. J. AUST., 2: 608.

FAGRAEUS, A. (1948), "Antibody Production in Relation to the Development of Plasma Cells", *Acta med. scand.*, 130: Suppl. 1, 7.

FLEISCHHAKER, H. (1940), *"Über die Plasmazellen und das retikuloendotheliale System des Knochenmarkes. Beitrag zur Herkunft der Plasmaeiweisskörper"*, *Dtsch. Arch. klin. Med.*, 186: 506.

FLEISCHHACKER, H. (1941), *"Über die Bedeutung der Retikuloendothelialen und Plasmazellen des Knochenmarks"*, *Ergebn. inn. Med. Kinderheilk.*, 60: 508.

FLYNN, F. V., and DE MAYO, P. (1951), "Microelectrophoresis of Protein on Filter Paper", *Lancet*, 2: 235.

GOOD, R. A., and CAMPBELL, B. (1950), "The Relationship of the Numbers of Bone Marrow Plasma Cells to the Concentration of Gamma Globulin in Rheumatic Fever", *Amer. J. Med.*, 9: 33.

GOOD, R. A. (1955), "Studies of Agammaglobulinæmia. II. Failure of Plasma Cell Formation in the Bone Marrow and Lymph Nodes of Patients with Agammaglobulinæmia", *J. Lab. clin. Med.*, 46: 167.

GORMSEN, H., and HEINZELMANN, F. (1941), "Behaviour of Sedimentation Reaction. Serum Proteins and Sternal Punctate in Serum Sickness", *Nord. Med.*, 11: 2125.

HOLMES, E. G., STANIER, M. W., SEMAMBO, Y. B., and JONES, E. R. (1951), "An Investigation of Serum Proteins of Africans in Uganda", *Trans. roy. Soc. trop. Med. Hyg.*, 45: 371.

JANSEN, A. A. J. (1959), "Nutrition, Infection and Serum Proteins in Papuans of Netherlands New Guinea", M.D. Thesis, Rototype, Broos, Amsterdam.

JENCKS, W. P., JETTON, M. R., and DURRUM, E. L. (1955), "Paper Electrophoresis as a Quantitative Method. Serum Proteins", *Biochem. J.*, 60: 205.

KARIKS, J., KOOPTZOFF, O., STEED, M., COTTER, H., and WALSH, R. J. (1960), "A Study of Some Physical Characteristics of the Goroka Natives, New Guinea", *Oceania*, 30: 225.

KARIKS, J., and HIPSLEY, E. H. (1961), "Serum Protein Levels in Mothers and New-born Infants — A Comparison of New Guineans with Australians", MED. J. AUST., 1: 853.

MARRACK, J. R., and HOCH, H. (1949), "Serum Proteins. A Review", *J. clin. Path.*, 2: 161.

NOSSAL, G. J. V. (1959), "Studies on the Transfer of Antibody Producing Cells to Young Animals", *J. Immunol.*, 2: 137.

NOSSAL, G. J. V. (1960), "Antibody Production by Single Cell. 4. Further Studies on Multiply Immunized Animals", *Brit. J. exp. Path.*, 41: 89.

OGRYZLO, M. A., McLACHLAN, M., DUPHINEE, J. A., and FLETCHER, A. A. (1959), "The Serum Proteins in Health and Disease", *Amer. J. Med.*, 27: 596.

PHILLIPS, R. A., VAN SLYKE, D. D., HAMILTON, P. B., DOLE, V. P., EMERSON, K., and ARCHIBALD R. M. (1950), "Measurement of Specific Gravities of Whole Blood and Plasma by Standard Copper Sulphate Solution", *J. biol. Chem.*, 183: 305.

STOBBE, H. (1960), "*Zum Sekretionsmechanismus der Plasmazellen*", *Schweiz. med. Wschr.*, 2: 1265.

TAUSSIG, A. F., and SAMOGYI, M. (1940), "Hyperglobulinæmia in Granuloma Inguinale", *J. Lab. clin. Med.*, 25: 1070.

VERA, J. E., and ROCH, M. (1956), "A Note on Distribution of Serum Protein Fractions in Apparently Normal Persons in Caracas", *J. Lab. clin. Med.*, 47: 418.

WILLS, E., and BELL, M. E. (1951), "The Serum Protein Levels in Samoans, Fijians and Indians in Fiji", *Lancet*, 1: 820.

WILKINSON, J. K., DAY, A. J., PETERS, J. A., and CASLEY-SMITH, J. R. (1958), "Serum Proteins of Some Central and South Australian Aborigines", MED. J. AUST., 2: 158.

THE EFFECT OF VITAMIN A AND VITAMIN D CAPSULES UPON THE INCIDENCE OF CORONARY HEART DISEASE AND BLOOD CHOLESTEROL.

By F. C. H. ROSS, M.B., B.S. (Melbourne),
Medical Officer, Repatriation Department,

AND

A. H. CAMPBELL, M.D. (Melbourne), M.R.A.C.P.,
Senior Specialist in Chest Diseases, Repatriation Department.

(*From the Repatriation Chest Clinic, Caulfield, Victoria.*)

DESPITE considerable interest in the relationship of cholesterol metabolism to coronary heart disease, investigation of the effect of vitamin A and vitamin D upon cholesterol metabolism and coronary heart disease has been incomplete and inconclusive.

The present investigation was conducted in a clinic primarily concerned with the management of chest diseases. For ten years one of us (F.C.H.R.) had used a vitamin A and vitamin D preparation in the treatment of certain patients. Advantage was taken of this circumstance to examine the long-term influence of the preparation upon the incidence of coronary heart disease. It became apparent that the patients treated with vitamin A and vitamin D capsules had a reduced incidence of coronary heart disease; consequently various possible explanations were considered. One of the more obvious questions was whether the vitamin preparation influenced cholesterol metabolism. Consequently, the effect of the preparation upon the serum cholesterol level was examined. Subsequently a search of the literature revealed evidence that vitamin A, rather than vitamin D, had a profound influence upon cholesterol metabolism.

Methods and Materials.

The effect of the vitamin A and vitamin D capsules upon the incidence of coronary heart disease was observed over five and a half years in 136 patients, with 271 patients serving as controls. With certain exceptions these were all the male patients in the clinic (of F.C.H.R.) in January, 1955, who were aged at least 45 years and had not had criteria of coronary heart disease. We have been successful in following all these patients until death or until June 30, 1960. There were approximately 20 other patients originally in the group who were lost to follow-up investigation. The number of exclusions is regarded as being too small to have influenced the results significantly.

The 407 patients were divided into two groups according to whether or not they had been prescribed one capsule containing vitamin A and vitamin D three times a day for at least six months during the period of observation between January, 1955, and June, 1960. Each capsule contained 6000 units of vitamin A and 1000 units of vitamin D in 0·1 ml. of peanut oil. A majority of the treated patients received the capsules for two to five years.

Quite independently of this investigation, the practice in the clinic had been to record and investigate electrocardiographically any evidence of coronary heart disease. Consequently the records were suitable for determination of the incidence of coronary heart disease.

For the purpose of this investigation, coronary heart disease was considered to have developed when any of the following criteria were present: (i) electrocardiographic evidence of typical myocardial infarction reported independently by a cardiologist; (ii) post-mortem evidence of myocardial infarction (of the patients followed, 77 died and on 24 autopsies were performed); (iii) sudden death certified by the attending medical practitioner as due to coronary heart disease, without post-mortem examination; (iv) protracted angina or cardiac deterioration requiring treatment in bed, with electrocardiographic evidence of transient ischæmia or coronary insufficiency; (v) typical angina pectoris on exertion with or without electrocardiographic changes.

For a case to be included as coronary heart disease, both of us had to agree with the diagnosis. Post-mortem evidence of coronary sclerosis alone or chronic cardiac failure without other evidence of coronary heart disease was not regarded as adequate grounds for inclusion.

Serum Cholesterol.

The effect of the vitamin A and vitamin D capsules upon serum cholesterol levels was examined in 20 males aged between 37 and 72 years. Thirteen of the subjects were attending the clinic as patients, and seven were on the staff. A group of 16 males on the staff, aged between 37 and 64 years, served as untreated controls.

Both groups continued their usual diets, and the serum cholesterol level was determined initially and subsequently after two and four weeks. During this period the 20 treated subjects were given capsules containing 6000 units of vitamin A and 1000 units of synthetic vitamin D dissolved in 0·1 ml. of peanut oil. Three capsules per day were prescribed. The serum cholesterol level was measured by means of a modified Lieberman Burchard reagent. The method (Newfield, to be published) avoids increased values for ester fractions. Duplicate results seldom vary by as much as 10 mg. per 100 ml. In the present investigation the means of the duplicate measurements were recorded. When the duplicates varied by more than 12 mg. per 100 ml., the estimations were repeated.

Results.

Incidence of Coronary Heart Disease.

Of the 407 patients observed for five and a half years or until death, 136 had received treatment with the vitamin A and vitamin D preparation for six months or longer, and 271 had not received the specified treatment. Of the treated group, 8 (5·8%) developed coronary heart disease compared with 43 (15·8%) of the control group. The difference is statistically significant ($\chi^2 = 7{\cdot}35$, $P < 0{\cdot}01$).

The cases were classified according to the type of coronary heart disease as follows: Group I: infarction with characteristic electrocardiographic or post-mortem evidence; Group II: probable infarction, with (*a*) electrocardiogram showing evidence of myocardial ischæmia

followed subsequently by death certified as being due to coronary heart disease without autopsy; (*b*) sudden death certified as due to coronary heart disease; Group III: intermediate group—protracted angina or cardiac deterioration requiring treatment in bed with electrocardiographic evidence of transient myocardial ischæmia or coronary insufficiency; Group IV: angina pectoris only, with or without electrocardiographic changes.

When this classification was applied (Table I), only two (1·5%) of the treated patients, compared with 23 (8·5%) of the controls developed coronary heart disease

TABLE I.
Number of Cases of Coronary Heart Disease in Various Classifications.

Subjects.	Proved Infarction.	Probable Infarction.	Intermediate Group.	Angina Pectoris.	Total.
Treated group (136 persons)	0	2	0	6	8
Untreated group (271 persons) ..	12	7	4	20	43

having the criteria of the combined Groups I to III above. The difference in the incidence of these more serious and less equivocal types of coronary heart disease is statistically significant ($\chi^2 = 6·6$, $0·01 < P < 0·02$). This helps to eliminate the possibility that the results were due to bias in the classification of doubtful cases of angina pectoris.

A comparison has been made of the mortality from various conditions in the treated and control groups (Table II). It is seen that there is a tendency for the treated group to have a lower mortality from cerebrovascular accidents as well as from coronary heart disease. Although the difference is not significant, when taken in association with the findings for coronary heart disease the trend suggests that a significant difference might be found in a larger series.

The deaths from various other causes are rather small, and there is no significant difference between the groups.

Effects of Vitamin A and Vitamin D on the Serum Cholesterol Level.

The vitamin preparation had a definite influence upon the serum cholesterol level, when this was initially above 250 mg. per 100 ml. No influence was observed on subjects with an initial cholesterol level of below 250 mg. per 100 ml. In 13 subjects with serum cholesterol levels of 250 mg. per 100 ml. or above, there was a mean reduction of 30·9 and 29·1 mg. per 100 ml. after two and four weeks respectively (Table III). By the use of the method of testing the significance of the difference between correlated means (McNemar, 1949), the difference between the initial serum cholesterol levels and the levels after two and four weeks is highly significant in both instances ($P < 0·001$). In contrast, in the untreated controls there was no significant alteration in the mean cholesterol levels after two and four weeks (Table III).

Comparability of the Two Groups Investigated for Coronary Heart Disease.

Although the vitamin preparation had been administered without any thought of preventing coronary heart disease, usually it had been administered when a patient's health was regarded as subnormal. To this extent only may the treated group be regarded as being selected. This has led to certain weight differences in the two groups. The weights had been recorded in 1955, but some difficulty was encountered in calculating the standard weights, as the deceased patients were no longer available for height measurement. Fortunately, in all but 19 of the 407 cases, it was possible to obtain the height from the service enlistment documents. Tables of the standard weight of Australian males according to height and age were used to determine the standard weight for each individual, and the actual weight was then expressed as a percentage of the standard weight. We do not regard the standard weight as being the desirable body weight, but it does provide a reference by which individuals of differing height and age can be compared in terms of a single variable of relative weight.

It was demonstrated that there were more individuals below their standard weight than above it, especially in the treated group (Table IV). This difference between the groups requires careful consideration. Dawber *et alii* (1957) found that individuals of substandard weight did not have any lower incidence of coronary heart disease than those of standard weight. Likewise, overweight carried little increased risk provided this was not more than 39% of the standard weight (Doyle *et alii*, 1957). In the present investigation the patients were in this neutral range, within which weight differences are unlikely to influence the incidence of coronary heart disease. This neutral effect could be substantiated in the present investigation. In the untreated group, the incidence of coronary heart disease for those of substandard weight was 16·6%, for those of standard weight 16·2%, and for those above standard weight 10% (Table V). For these reasons, the observed weight difference can be regarded as being within a neutral range incapable of causing the difference in coronary heart disease between the two groups.

During the period of observation, the treated group contained a slightly higher percentage of individuals with active tuberculosis (29%), compared with the controls (15%). The incidence of coronary heart disease was slightly lower in those with active disease compared with those with inactive tuberculosis; this difference was not statistically significant. Therefore, the small difference between the two groups is unlikely to have produced the observed difference in coronary heart disease incidence. Moreover, if the patients with active tuberculosis are excluded, there is still a significant difference in incidence of coronary heart disease between the treated groups and the controls. Consequently the influence of active tuberculosis can be excluded as an explanation of the difference in the incidence of coronary heart disease.

The two groups were closely similar in age distribution (Table VI).

Discussion.

This investigation was conducted upon persons 90% of whom had previously had tuberculosis. It is not anticipated that this would have influenced the incidence of coronary heart disease, as in a study of a large group of tuberculous persons in Queensland, Victoria and Western Australia, the mortality from coronary heart disease was not significantly different from the expected mortality (Campbell, 1961). Consequently the incidence of coronary heart disease in the untreated group in this investigation is likely to have been the same as that in the

TABLE II.
Causes of Death.

Subjects.	Coronary Heart Disease.	Other Heart Diseases and Disease of Aorta.	Cerebrovascular Accidents and Hypertension.	Tuberculosis.	Other Chest Conditions.	Gastro-Intestinal Disease.	Malignant Disease.	Renal Disease.	Accidental.	Total.
Treated group (136 persons)	2	3	3	6	2	1	3	0	1	21
Untreated group (271 persons)	10	5	10	7	5	3	13	2	1	56

TABLE III.

Effect of Vitamin A and Vitamin D Capsules on Blood Cholesterol Level.

Subjects.	Number.	Mean Serum Cholesterol Level (mg. per 100 ml.).			Significance.
		Initial.	After 2 Weeks.	After 4 Weeks.	
Treated group: initial serum cholesterol level 250 mg. per 100 ml. and above.	13	301·5	270·6	272·4	(i) "Initial" versus "2 weeks", reduction of 30·9 mg. per 100 ml.; $t=5·05$, $n=12$, $P<0·001$; highly significant. (ii) "Initial" versus "4 weeks", reduction of 29·1 mg. per 100 ml.; $t=5·22$, $n=12$, $P<0·001$; highly significant.
Treated group: initial serum cholesterol level 249 mg. per 100 ml. and below.	7	229·7	225·1	238·0	(i) "Initial" versus "2 weeks", reduction of 4·6 mg. per 100 ml.; $t=0·42$, $n=6$, $0·7>P>0·6$; not significant. (ii) "Initial" versus "4 weeks", increase of 8·3 mg. per 100 ml.; $t=0·74$, $n=6$, $0·6>P>0·5$; not significant.
Untreated controls	16	273·1	278·1	284·0	(i) "Initial" versus "2 weeks", increase of 5 mg. per 100 ml. $t=0·6$, $n=15$, $0·6>P>0·5$; not significant. (ii) "Initial" versus "4 weeks", increase of 10·9 mg. per 100 ml.; $t=1·6$, $n=15$, $0·2>P>0·1$; not significant.

general population. This conclusion is supported by estimating the expected incidence of coronary heart disease from figures based upon American experience. Although these cannot be uncritically applied to the Australian scene, both countries have a high and reasonably similar mortality from coronary heart disease. Consequently, it can be predicted that the incidence in each country will be similar.

In the Framingham (U.S.A.) investigation (Dawber *et alii*, 1957), the incidence of coronary heart disease was found to be 2·5% *per annum* for males between the ages of 55 and 62 years. In the present investigation, the ages overlap both the upper and lower age to an equal extent. On the assumption that these differences had a cancelling effect, the incidence of coronary heart disease in the present investigation should have been of the same order as those of the Framingham study. On the basis of the American investigation, the incidence of coronary heart disease would be 14%, compared with an actual incidence of 15·8% amongst the controls and 5·8% amongst the treated group. This suggests that the difference in the incidence of coronary heart disease between the controls and the treated groups is due to an actual reduction in the incidence in the treated group, and not to an increased incidence amongst the controls.

In the absence of random allocation of cases to the treated group, it cannot be claimed with absolute finality that the reduced incidence of coronary heart disease was due to the vitamin A and vitamin D preparation. However, there is no other obvious explanation. In addition, the lowering of abnormal serum cholesterol levels by the vitamin A and vitamin D supplements supports the observation that the incidence of coronary heart disease is reduced in persons receiving vitamin A and vitamin D supplements. Investigations in progress suggest that the reduction in the cholesterol level can be sustained. The present results are consistent with the important observations of Kinley and Krause (1959), who found a mean reduction of 71 mg. per 100 ml. in the serum cholesterol level when vitamin A was administered for four to six months to eight persons who had suffered recent myocardial infarction and had an elevated mean serum cholesterol level of 355 mg. per 100 ml. Corresponding with our failure to influence serum cholesterol levels of 249 mg. per 100 ml. or below in the present investigation, Kinley and Krause found no significant change in a small group with an initial mean cholesterol level of 240 mg. per 100 ml.

Possible Mode of Action.

The capsules administered contained vitamin A and vitamin D and a small quantity of peanut oil. Although the last-mentioned contains unsaturated fatty acids, which may affect cholesterol metabolism when administered in sufficient quantities, the total peanut oil administered daily (0·3 ml.) is much smaller than the amount usually considered necessary to produce any significant influence upon either the blood cholesterol level or the incidence of coronary heart disease.

Experimentally, vitamin D in excess elevates the plasma cholesterol level and promotes atheroma (DeLangen and Donath, 1956). Although these results are not necessarily applicable to humans, they suggest that vitamin D is unlikely to reduce either the serum cholesterol level or the incidence of coronary heart disease. However, further investigation is indicated before vitamin D can be excluded as a direct or synergic factor.

Because of its importance in the health of epithelial cells, the effect of vitamin A upon endothelial cells requires reexamination. Also it is possible that vitamin A has some influence on fibrous tissue in the intima of blood vessels, as it diminishes fibrosis in tissue culture (Fell, 1957). What is more important, vitamin A has been shown to influence cholesterol metabolism and to reduce experimental atheroma. Weitzel *et alii* (1955) reported that vitamin A had a definite protective effect on experimental atherosclerosis in hens. Later, Weitzel *et alii* (1956) reported that when vitamin A was given to old atherosclerotic hens, there was a pronounced regression of the atheromatosis in all the test groups and a decrease in the total fat content of the aorta. This effect was enhanced when vitamin E was given with vitamin A, but when given alone vitamin E had little effect. Recently Wood (1960) has made the important observation that vitamin A prevented the hypercholesterolæmia induced by feeding cholesterol to chicks. Kinley and Krause (1959) have reported the lowering of the blood cholesterol level of "atheromatous" patients treated with vitamin A.

Recently, Schettler *et alii* (1960) examined, in a double blind trial, the influence of vitamin A plus vitamin E upon established atherosclerosis of humans. In cerebrovascular sclerosis, coronary heart disease and peripheral vascular disease, symptoms attributable to ischæmia were relieved more frequently by vitamin A plus vitamin E than by a placebo. However, this was not statistically

TABLE IV.

Numbers of Individuals with Weight Variation from Standard Weight Shown as Percentage of Difference.

Subjects.	Plus 30% to 39%.	Plus 20% to 29%.	Plus 10% to 19%.	Plus or Minus 9%.	Minus 10% to 19%.	Minus 20% to 29%.	Minus 30% to 49.%	Total.[1]
Treated group	0	0	0	56	49	21	5	132
Untreated group	4	7	19	136	51	35	5	256

[1] Owing to incomplete data, 19 subjects in the original groups have not been classified.

significant except for the group as a whole; 37% were improved with vitamin A plus vitamin E, compared with 26% improved with a placebo. When vitamin B_6 was added to the vitamin A plus vitamin E, the results were not significantly different from those with the placebo. This investigation is not entirely conclusive, owing to some obscurity in the statistical analysis and the lack of many objective changes. However, oscillometry showed 100% increase of pulsation in 12% each of patients given vitamin A plus vitamin E and vitamin A plus vitamin E plus vitamin B_6, but in only 2% of patients receiving the placebo. Also German ophthalmologists have observed improvement in the condition of arteriosclerotic retinal vessels following treatment with vitamin A plus vitamin E. These findings suggest that vitamin A plus vitamin E may reduce atherosclerosis in humans.

TABLE V.

Incidence of Coronary Heart Disease According to Relative Weight.[1]

Subjects.	Over Standard Weight.	Standard Weight.	Under Standard Weight.
Treated group (132 persons)..	—	5·4%	4·6%
Untreated group (256 persons)	10%	16·2%	16·6%

[1] Owing to incomplete data, 19 subjects have been excluded from the original groups.

All these observations support our present findings, and suggest that vitamin A, rather than vitamin D, is the more likely agent to have reduced the incidence of coronary heart disease and lowered the serum cholesterol level.

As vitamin A appears to be capable of correcting an abnormal cholesterol metabolism, it is necessary to consider whether such abnormality was, in the first place, due to a relative deficiency of the vitamin. This seems very probable, as Ralli and Waterhouse (1933), Smith (1934) and Mayer and Truant (1949) have observed elevated blood cholesterol levels in vitamin-A-deficient animals. Ralli and Waterhouse found that the administration of carotene to one, and concentrated cod-liver oil to another, of two vitamin-A-deficient dogs, produced a marked fall in blood cholesterol to normal levels. In both instances there was an initial over-correction of the blood cholesterol level. The failure of Sure *et alii* (1933) and of Green *et alii* (1955) to detect significant alterations in the blood cholesterol level may have been due to variation of other factors, as the observations of Wolf *et alii* (1957) with carbon-14 provide good evidence of excess synthesis of cholesterol and fatty acids in vitamin-A-deficient animals. Also, it is of interest that vitamin A has a chain structure closely related to farnesoic acid, and its analogues, which have been shown by Popjak *et alii* (1960) to inhibit cholesterol synthesis *in vitro*. The evidence suggests that when vitamin A corrects an abnormal cholesterol metabolism, or reduces atheroma or the incidence of coronary heart disease, it does so because the corrected abnormalities were caused by a relative vitamin A deficiency. If this is correct, the substantial reduction in the incidence of coronary heart disease and the tendency for the serum cholesterol level to be reduced by the capsules indicate that vitamin A deficiency must be rather frequent in middle-aged and elderly males.

Examination of the amounts of vitamin A available for consumption suggests that large sections of the population could have a low intake. The amount of vitamin A available for daily consumption per head of the Australian population was 7501 I.U. in 1958-1959. (Commonwealth Bureau of Census and Statistics, 1958-1959.) This is based upon foods available for consumption, which is not the same as the food consumed. The Food and Agriculture Organization of the United Nations estimates that up to 15% of food available may be wasted in communities with a plentiful food supply. Consequently, the amount of vitamin A actually consumed is likely to be only 6376 I.U. Although this is higher than the recommended allowance of 4450 I.U. per head, the minimal requirements of vitamin A are not known with certainty, and the recommended figure may be too low to prevent a disordered cholesterol metabolism in older persons on a diet of high fat content. Moreover, the calculated figures, being averages, give no information regarding the food consumption of individuals or of specific groups of the population. It can be taken for granted that individual consumption of vitamin A will be scattered about the average. As this average is reasonably close to the estimated requirements, and as the largest source of vitamin A is from the least popular vegetables, it can be presumed that many individuals consume less than the estimated requirements.

Owing to the relatively narrow range of foods with a high vitamin A content, food preferences can lead to a low vitamin A intake even in high income groups. In Australia and America, owing to changing food habits, there has been a very definite fall in vitamin A consumption per head in the last 20 to 30 years. (U.S.A.: before the war, 8200 I.U.; 1959, 7200 I.U.; Australia: before the war, 8457 I.U.; 1958-1959, 7501 I.U.). In Australia this fall is due largely to the reduced consumption of carrots, leafy greens and other fresh vegetables.

It is of interest also that in under-developed countries such as New Guinea with a low incidence of coronary heart disease, the vitamin A intake is high, owing to the vegetarian diet containing sweet potato, which is rich in vitamin A. Of course, the fat-poor diet may be equally important in such groups, but the Eskimos, who are reputed to have a fat-rich diet with a low incidence of coronary heart disease, have a high vitamin A intake from fish and marine animal livers. Thus, some of the facts revealed by epidemiological studies concerning coronary heart disease are not inconsistent with vitamin A deficiency playing an important rôle in high-income countries as opposed to less developed areas. A fat-rich diet, of course, may be a contributing factor in the presence of vitamin deficiency, and it is not suggested that a deficiency of either vitamin A or vitamin D is the sole factor in the development of coronary heart disease. Although further large-scale investigation will be necessary to determine the general importance of vitamin A (and vitamin D) deficiency in the genesis of coronary heart disease, vitamin A deficiency is likely to have been a frequent cause of coronary heart disease in the individuals investigated.

Summary.

The incidence of coronary heart disease over a period of five and a half years in a group of 136 patients receiving vitamin A and vitamin D capsules for between six months and five and half years was compared with that of 271 controls attending the same clinic.

Of the treated group, eight (5·8%) developed coronary heart disease, compared with 43 (15·8%) of the control group. The difference is statistically significant. Of the more serious and less equivocal types of coronary heart disease, there were only two (1·5%) cases amongst the

TABLE VI.

Percentage of Each Group in Various Age Groups.

Subjects.	Years.						
	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 and Over.	Total.
Treated ..	5·9	9·7	31·1	31·8	14·1	7·4	100
Untreated ..	9·7	11·1	25·7	30·1	16·0	7·4	100

treated group and 23 (8·5%) amongst the controls. The difference is significant. Following administration of the vitamin A and vitamin D preparation, there was a highly significant reduction ($P < 0.001$) of the mean serum cholesterol level in a group of 13 males with an initial level of 250 mg. per 100 ml. or more. There was no significant change in the mean cholesterol level of seven males with an initial level of 249 mg. per 100 ml. or less.

As there is independent evidence that vitamin A deficiency causes an abnormal cholesterol metabolism, and that vitamin A supplements are antihypercholesterolæmic and can reverse atheroma experimentally, vitamin A is likely to be the active substance in the capsules. It was concluded that, in the group investigated, relative vitamin A deficiency was likely to have been an important cause of coronary heart disease.

Acknowledgements.

We wish to thank Miss M. K. Paxton and Dr. A. R. Parkin, of the Repatriation Pathological Department, for their cooperation, Mr. J. W. Legge, Reader in Biochemistry, University of Melbourne, for his helpful advice, and the Chairman of the Repatriation Commission for permission to publish this paper.

References.

CAMPBELL, A. H. (1961), "The Association of Lung Cancer and Tuberculosis", *Aust. Ann. Med.*, 10: 129.

COMMONWEALTH BUREAU OF CENSUS AND STATISTICS (1958-1959), "Report on Food Production and the Consumption of Foodstuffs and Nutrients in Australia", Canberra, No. 14.

DAWBER, T. R., MOORE, F. E., and MANN, G. V. (1957), "Coronary Heart Disease in the Framingham Study", *Amer. J. publ. Hlth*, 47: Supplement, 4.

DELANGEN, C. D., and DONATH, W. F. (1956), "Vitamin D Sclerosis of the Arteries and the Danger of Feeding Extra Vitamin D to Older People, with a View on the Development of Different Forms of Arteriosclerosis", *Acta med. scand.*, 156: 316.

DOYLE, J. T., HESLIN, H. E., HILLEBOE, P. F., FORMAL, P. F., and KORNS, R. F. (1957), "Prospective Study of Degenerative Heart Disease in Albany: Report of Three Years' Experience. 1. Ischæmic Heart Disease", *Amer. J. publ. Hlth*, 47: Supplement, 25.

FELL, H. B. (1957), "The Effect of Excess Vitamin A on Cultures of Embryonic Chicken Skin Explanted at Different Stages of Differentiation", *Proc. roy. Soc.*, Series B, 146: 242.

GREEN, B., LOWE, J. S., and MORTON, R. A. (1955), "The Effect of Vitamin A Deficiency on the Cholesterol Levels of the Plasma and Liver of the Rat", *Biochem. J.*, 61: 447.

KINLEY, L. J., and KRAUSE, R. F. (1959), "Influence of Vitamin A on Cholesterol Blood Levels", *Proc. Soc. exp. Biol. (N.Y.)*, 102: 353.

MAYER, J., and TRUANT, A. P. (1949), "Effects of Administration of Testosterone on Vitamin A Deficient Rats", *Proc. Soc. exp. Biol. (N.Y.)*, 72: 436.

MCNEMAR, Q. (1949), "Psychological Statistics", Wiley, New York: 225.

POPJAK, G., CORNFORTH, R. H., and CLIFFORD, K. (1960), "Inhibition of Cholesterol Biosynthesis by Farnesoic Acid and its Analogues", *Lancet*, 1: 1270.

RALLI, E. P., and WATERHOUSE, A. (1933), "Blood Cholesterol in Dogs on an A Deficient Diet", *Proc. Soc. exp. Biol. (N.Y.)*, 30: 519.

SCHETTLER, G., KIRSCH, K., HUHN, E., KNEDEL, M., OTT, H., SCHÜSSEL, H., SCHÖLMERICH, P., and GUNTHER, W. (1960), *"Die Vitamine A + E + B6 in der Behandlung der Arteriosklerose", Dtsche med. Wschr.*, 85: 732.

SMITH, M. E. (1934), "The Effect of Vitamin A Deficiency on the Concentration of the Blood Lipids of Albino Rats", *J. Nutr.*, 6: 675.

SURE, B., KIK, M. C., and CHURCH, A. E. (1933), "Avitaminosis XIV. Effect of Vitamin A Deficiency on Concentrations of Blood Lipids of Albino Rats", *Proc. soc. exp. Biol. (N.Y.)*, 30: 620.

WEITZEL, G., SCHÖN, H., and GEY, F. (1955), *"Anti-atherosklerotische Wirkung fettlöslicher Vitamine", Klin. Wschr.*, 33: 772.

WEITZEL, G., SCHÖN, H., GEY, F., and BUDDECKE, C. (1956), *"Fettlösliche Vitamine und Atherosklerose", Z. physiol. Chem.*, 304: 247.

WOLF, G., LANE, M. D., and JOHNSON, B. C. (1957), "Studies on the Function of Vitamin A in Metabolism", *J. biol. Chem.*, 225: 995.

WOOD, J. D. (1960), "Dietary Marine Fish Oils and Cholesterol Metabolism. 2. The Effect of Vitamin A and Lingcod Liver Oil Components on the Serum Cholesterol Level in Chicks", *Canad. J. Biochem.*, 38: 879.

EMBOLECTOMY AND RETROGRADE FLUSH: CONSIDERATION OF THE REASONS FOR AN AGGRESSIVE ATTACK ON ACUTE THROMBO-EMBOLISM.

By WALTER BURFITT-WILLIAMS, F.R.C.S. (Eng.), F.R.C.S. (Edin.),

Clinical Assistant Surgeon, St. Vincent's Hospital; Clinical Assistant Surgeon, Royal Alexandra Hospital for Children, Sydney.

FRANK LAHEY in 1926 wrote concerning peripheral arterial embolectomy: "The experience with this operation has convinced us of the soundness of the procedure and we believe will enable us to conserve some extremities also." His optimism is confirmed today.

However, as some clinicians would still hesitate to consider embolectomy, it seems appropriate to point out the fallacies of the argument for conservative treatment, review the literature that bears on this problem and present the rationale for the modern treatment of acute peripheral arterial block.

The argument for conservative treatment is based on statistics. McGarity (1958) reviewed the literature and showed that in 580 femoral embolectomies success was achieved only in 35%. Jacobs (1958) states that of seven collected series only one claims a survival rate over 50%, while the corresponding figure for untreated embolism is 71%.

What is wrong with these figures? Firstly, the series are not comparable because one finds (as expected) that those patients submitted to surgery are the worst cases — those that had no chance of limb survival with medical treatment and those in whom medical treatment had failed.

Secondly, series of 20 or even 10 years ago cannot be compared with series of today. For example, let us examine one of the largest and most successful series reported by Warren *et alii* (1954) from the Massachusetts General Hospital. Their cases are divided into two series: those from 1937 to 1946, and those from 1946 to 1953. In the more recent series the mortality has dropped to 28% from 36% in the earlier series and the limb survival has risen to 86% compared with 66% previously.

These are combined series of medically and surgically treated cases, but three important facts emerge on analysis of the results: firstly, a 100% improvement in early referral of patients has resulted from education of the local practitioners; secondly, the number of patients treated surgically has more than doubled in the more recent series; thirdly, more thorough operations are being performed.

To determine the rational management of this problem let us consider the ætiology, pathology and clinical features of peripheral arterial embolism and then discuss the treatment.

Ætiology.

The most common site of origin of an embolus is the left side of the heart. Over 50% arise in the left atrium in association with auricular fibrillation, and mural thrombus in the left ventricle due to myocardial infarction is the next commonest cause (Warren, 1954; McGarity, 1958). Less commonly emboli arise from vegetations on heart valves and atheromatous plaques in the great vessels. Rare causes are tumours, foreign bodies and paradoxical emboli. Spontaneous thrombosis on an atheromatous plaque may mimic embolism.

The reason for dislodgement of an embolus is not always obvious, but trauma, especially surgery, and changes in rhythm play a part in some cases.

Pathology.

Emboli lodge at points of narrowing in the arterial tree — that is, at bifurcations or where main branches are given off—for example, the aortic, iliac, common femoral[1] and

[1] The term "common femoral", though no longer used by anatomists, is of great importance clinically. In modern terminology the common femoral bifurcation is the point where the femoral artery gives off its profunda branch.

popliteal bifurcations and the point where the axillary artery gives off its subscapular branch.

The result of lodgement of an embolus depends upon the effect it has on the distal circulation. Spasm, consecutive thrombosis, the anatomy of the collateral circulation and the state of the arterial wall and cardio-vascular system generally must all be considered.

Spasm.

The cause of proximal and collateral arterial spasm is not understood. That it occurs in association with vessel injury (for example, in supracondylar fractures of the humerus) is known, but its absence at embolectomy operations has been frequently seen. Jacobs considers that "many of the statements made about embolic arteriospasm do not seem to be well substantiated". Serotonin released from platelets involved in the thrombus has been suggested (Aniyan and Hart, 1957) as a causative factor.

Consecutive Thrombosis.

Distal thrombosis following obstruction of a main vessel is unpredictable. Early workers (Key, 1922) found secondary thrombosis as early as two hours after embolism in some cases, but in others did not observe it after a prolonged interval. This is confirmed in most surgeons' experience.

Proximal thrombosis may occur in the stagnant column of blood between an embolus and the next proximal major branch.

The pathology of thrombosis is not completely understood but the following factors are clinically significant: (i) The rate of flow. Distal to an occlusion this is determined by the collateral circulation. (ii) Time is important. The better over-all results of early operation are ascribed to the restoration of flow before thrombosis occurs (Warren *et alii*, 1954), especially involving the collateral channels, which remain patent till late (Shaw, 1956). (iii) Disease of the vessel wall plays a part. Atheroma especially will predispose to thrombosis. Initially it affects the larger vessels and is a "segmental" disease, so that the collateral arterioles will escape. Later, when disease is generalized, any interruption of the circulation produces rapidly spreading thrombosis and gangrene — for example, in embolism on top of chronic ischæmic disease.

Collateral Circulation.

By post-mortem arteriography in a series of 66 human subjects, Olovson (1941) showed that deficient collateral circulation is rare in the popliteal and brachial systems but not uncommon in the femoral region. These findings correspond with the results of medical treatment.

Combined with the fact that the collateral channels are late to be affected by degenerative disease and consecutive thrombosis, it can be concluded that herein is the most important factor determining the outcome of vascular occlusion.

Vascular and Cardiac State.

That the state of the cardio-vascular system plays a part in the outcome of any clinical condition is obvious. Considering the ætiology of emboli one expects some patients, on presentation, to show impaired cardiac function due to infarction or decompensation due to valvular disease, and the odds against a successful outcome in such cases must be high. They make up an unavoidable or expected mortality in any series.

Clinical Features.

Severe acute peripheral arterial ischæmia is characterized by a classical clinical triad—pain, pallor and paralysis—and absent arterial pulses below the occlusion. Sudden onset of the three "P's" in a limb invariably means acute obstruction of the main artery.

The qualification "severe" is used because occlusion of a main vessel may be completely asymptomatic (with obviously minimal ischæmia). Jacobs (1959) examined the limb pulses of 269 patients with mitral stenosis and 300 controls. He found that 0·6% of the controls, 4·0% of the mitral stenotics with normal rhythm and 27·0% of the latter with fibrillation had old occlusions. In other words spontaneous recovery or completely silent occlusions can occur. As clinicians, we are interested in symptoms and signs and especially those that help in diagnosis and treatment. Let us therefore examine the above triad more closely.

Pain.

The site of the initial pain in an acute occlusion is frequently significant. The first symptom noticed by the patient may be a local, sharp, burning or stinging pain. If it can be localized by the patient when the doctor examines him, even though it has then passed off, it usually indicates the actual site of occlusion. This pain is quickly followed by that due to ischæmia in the tissues distal to the block. The latter pain is severe, cramping or aching and requires morphine for its relief. As paralysis develops the pain may diminish in its extent, but it still persists in the frontier zone if gangrene develops.

Pallor.

Coldness and dead whiteness develop in the area where there is no circulation at all, while the intermediate zone shows a blotchy, grey-purple cyanosis. Occlusion of the circulation will also be indicated by empty superficial veins and the absence of bleeding on pin prick.

Paralysis.

Both sensory and motor paralyses indicate severe ischæmia and death of the part if circulation is not restored very rapidly.

Gradation of Symptoms.

The triad of pain, pallor and paralysis indicates complete ischæmia. As has been mentioned above, arterial occlusion may be found with no symptoms at all, so that all grades of this triad may be met, depending upon the degree of circulatory obstruction. Pain on exercise may be the only symptom.

Similarly a proximo-distal gradient of symptoms and signs can be detected in an occluded limb. The level of these signs should be noted so that the effect of treatment may be ascertained, especially if one is trying medical measures, as they indicate the state of the blood supply at any level. Colour, temperature, sensation and movement will be the chief signs upon which the efficiency of treatment can be assessed, as pain should be controlled by analgesics and so give a false indication.

Treatment.

So many factors come into the picture that it is obvious that each case must be considered individually. The following scheme of assessment and management based on the pathology and natural history of the disease is suggested.

Diagnosis.

The diagnosis should be easy on the physical signs and absent peripheral pulses, if one keeps in mind the presence of disease associated with emboli and the fact that emboli lodge at points of bifurcation in main vessels.

General Management.

The relief of pain, the treatment of shock and the assessment of the patient as a whole is the next step. Remembering the possibility of multiple emboli (especially abdominal), a rapid assessment of the patient should be made and a suitable analgesic administered (morphine or pethidine), preferably intravenously in view of the urgency of the situation and the poor circulation in many cases. Shock is sometimes present and requires pressor drugs or intravenous therapy, depending upon the state of the heart. One has seen oligæmic shock, in a patient with poor peripheral circulation, mimic thrombo-embolic occlusion and the circulation recover after transfusion. Also it is important that the blood pressure be maintained if the collateral circulation is to function.

The cardiac condition must be assessed and its treatment commenced *pari passu* with that of embolism and shock.

Local Management.

All degrees of ischæmia can occur, and the local management is considered under the following headings: (i) prevention of further damage to the ischæmic part; (ii) prevention of increasing ischæmia; (iii) restoration of the circulation.

Prevention of Further Damage.—Trauma and infection are the two extraneous factors to which ischæmic tissues are immediately vulnerable. Both can be prevented by careful nursing and padded support to keep the skin dry and intact. Antibiotics are best withheld until their use is indicated.

Prevention of Increasing Ischæmia.—Extension of the thrombotic process is the chief cause of increasing ischæmia, therefore the early administration of anticoagulants is obvious. Heparin (10,000 units by intravenous injection) is given as soon as the diagnosis of an embolus is made. Whether it will prevent consecutive thrombosis must depend upon its reaching the distal circulation in adequate amounts. Cooling reduces ischæmia relatively, as metabolic activity is related to temperature. The posture of the part should be comfortable for the patient, but it should not be elevated. Elevation increases the venous return, diminishing the amount of blood in the limb, and must increase the resistance to inflow.

Restoration of Circulation.—If the collateral circulation is adequate to keep the part alive, heparin prevents extension of thrombosis while the embolus is organizing and, in some cases, canalizing. In almost all occlusions in the upper limb, administration of anticoagulants is all that is required. Doubt concerning the significance of spasm has been discussed under the heading of pathology, but let us consider the measures suggested to overcome spasm. These are: (i) reflexly, by warming the rest of the body; (ii) by vasodilator drugs (priscol or papaverine); (iii) by sympathetic block; (iv) by spinal anæsthesia. The usefulness of the first two methods is open to question because they aim at bringing about vasodilatation throughout the body. This will result in a fall of blood pressure and probably a reduction in blood flow through the collateral circulation. This objection is not valid if local sympathetic block by injection or spinal anæsthesia is used. However, what is the effect of this? The most marked effect is on the skin vessels. Thus such blood as is now reaching the part through the collateral circulation is diverted to the surface, reducing the pressure and flow in the main vessels. Moreover sympathetic block is not easy to perform accurately. For example, to denervate the buttock area for iliac or femoral occlusion the sympathetic trunk must be paralysed to the tenth thoracic ganglion (Rob, 1957, quoted by Mavor, 1958). What then is the place of sympathectomy and vasodilators in acute arterial occlusion? General vasodilatation by reflex warming or drugs has nothing to recommend it. Local vasodilatation by sympathetic block has been credited with good results. Probably it helps in those cases where survival of the limb would occur anyway and acts in the same way that sympathectomy relieves rest pain in chronic ischæmic disease. If spasm is really significant would not the best treatment be direct attack on the artery, as in acute brachial spasm associated with supracondylar fractures in the upper limb?

Operation. Embolectomy and Retrograde Flush.

Discussion.

In the last two decades much has been learned about the treatment of chronic peripheral arterial disease. In dealing with chronic ischæmia, sympathectomy, replacement grafts, by-pass grafts and endarterectomy have all been tried to restore the distal circulation. Sympathectomy is of least value in main-vessel occlusion and of maximum usefulness in small-vessel disease (Ross, 1944). A local endarterectomy gives the best long-term results, when it can be performed.

It seems reasonable that removal of an embolus, which is a localized obstruction, should give the same result. One must therefore consider why the results of embolectomy have been so poor in the past.

Recent reports (Olivin *et alii*, 1953; Crawford and DeBakey, 1956; Shaw, 1956; Martin, 1958) would appear to give the explanation. Failure of embolectomy has been due to inadequate operations. When the embolus has been removed the vessel beyond is often still occluded by consecutive thrombus or other emboli. To restore the circulation the latter must also be removed. This may be achieved by massage, suction or retrograde flushing back through a peripheral vessel. The latter is probably the best method, as it demonstrates that the vessel is clear and also enables arteriotomy for removal of an embolus to be made more proximally in a larger vessel—for example, the femoral, when the site of occlusion is in a relatively small vessel, such as the popliteal, where thrombosis may follow suturing (Crawford and DeBakey).

Olivin *et alii* showed that good results, even in late cases after 48 hours, could be obtained when the distal circulation was cleared by suction or flushing. They reported recovery in five out of six cases, but one patient died later from uræmia (probably due to products released from the limb after delayed restoration of circulation in the presence of already damaged kidneys). Following Olivin's report, Shaw reported success in 13 out of 14 cases of acute ischæmia using embolectomy, endarterectomy or even resection according to circumstances, combined with removal of the distal clot. Crawford and DeBakey report success in 11 out of 12 cases using the retrograde flush technique and Martin reports success in seven out of eight cases with a similar method.

While these are only small series, they represent some of the worst cases and nothing, except amputation, would have been done for them only a few years ago.

Moreover, embolectomy is a relatively minor procedure. It can be easily performed under local anæsthesia with a minimum disturbance to the patient, and even in a chronically ill patient may save the additional disaster of a gangrenous limb.

Indications for Operation.

These may be considered as absolute and relative according to the severity of ischæmia. The absolute indication for surgery is the failure of conservative treatment and the certainty that the part will not survive unless the obstruction is removed. But operation must not be delayed while medical means are tried, only to be called upon when irreparable damage has occurred. Obviously a limb that is bloodless and paralysed will not recover by medical means. Therefore some more precise indications for surgery are warranted. Considering the natural recovery rate from past experiences published in the literature, it can be stated that aortic, iliac and femoral occlusions should all be submitted to operation. In popliteal thromboembolism and in occlusion in the upper limb each case must be judged on its merits. If paralysis is present the degree of ischæmia is severe. If there is no appreciable recovery one hour after the administration of heparin and analgesics and the restoration of the blood pressure, operation should be considered.

Shaw states that:

> The indications for embolectomy should be more liberal for two reasons: First, embolectomy can be applied to cases with extension of thrombus since extensive distal thrombus can often be successfully removed. Second, the operation should be performed even in cases in which limb survival is not in doubt since the incidence of chronic ischæmic symptoms in those patients who are treated "successfully" without an operation is high.

Urgency of Operation.

Complete recovery of function can be obtained only if the circulation is restored before consecutive thrombosis involves minor vessels and before tissue damage develops. If irreversible damage has occurred, fibrosis with ischæmic contraction will develop, even though arterial pulses are completely restored.

Even though successful late operations have been performed, embolectomy should always be regarded as a procedure of the greatest urgency and delay of even an hour may mean the difference between success and failure.

The following case is reported because it demonstrates the aggressive surgical treatment of peripheral arterial embolism.

A male, aged 78 years, a retired farmer, was admitted to the Royal Alexandra Hospital, Rhyl, North Wales, at midnight on August 3, 1958, with a history of sudden onset of pain and paralysis in the right leg, two hours before admission. The doctor who referred him to hospital stated that the patient had been fibrillating, but on admission his pulse was regular and remained so during the whole of his stay in hospital. The patient was also stated to have a carcinoma of the lower third of the œsophagus diagnosed elsewhere 18 months before on a barium-swallow X-ray examination and considered unfit for operation.

On examination, the patient was a wiry old man, slightly dehydrated but otherwise fit-looking, and not what one would have expected had he had a carcinoma of the œsophagus for 18 months.

Local examination revealed the classical triad of pain, pallor and paralysis in the right thigh, leg and foot, with absent pulses. No pulsation could be felt in the right groin or below. Pulses in the left lower limb were normal.

A diagnosis of right common iliac embolism was made, morphine (one-sixth of a grain) was given intravenously and the patient was taken to the operating theatre. Blood grouping was carried out and a slow intravenous saline infusion was commenced in case of accident. At 1 a.m. on August 4, a right common iliac embolectomy was performed under local anæsthesia by a transperitoneal approach through a right paramedian lower abdominal incision. The first and most important thing noticed was the normal pale-pink colour and elastic feel of this patient's arteries and the absence of hard or calcified plaques. The embolus, which was localized, as expected, at the right common iliac bifurcation, was removed through a common iliac arteriotomy after the common, internal and external iliac arteries were controlled with tapes and after heparin was injected to prevent clotting in each.

By the momentary release of the proximal tape after removal of the embolus any clot above was washed out. On the release of the distal tape no back bleeding occurred and a Desjardin's forceps passed down the external iliac artery revealed distal thrombus to be present, even though it was less than four hours since the embolism occurred. After as much clot as possible had been extracted, the iliac arteriotomy was closed and the tapes were released. Pulsation returned as far as the common femoral bifurcation, but not distally.

Having read that Shaw had removed distal thrombus up to 48 hours after embolism by retrograde flushing with heparin and saline, the surgeon decided to try this method. A femoral arteriotomy was performed and the dorsalis pedis artery in the foot was exposed (the posterior tibial artery at the ankle might have been better, as it is slightly larger). A "Polythene" catheter was inserted and tied in the artery exposed in the foot and heparin-saline (5000 units per pint) was injected under pressure. A clot 20 inches in length with a bifid tail (presumably from the anterior and posterior tibial arteries) was now removed intact through the femoral arteriotomy by gentle traction. Upon the closure of the femoral arteriotomy a normal politeal pulse was present and colour returned to the leg as far as the ankle. Over the next 12 hours the circulation returned also to the foot.

One week and three weeks later œsophagoscopy and dilatation of a short fibrous stricture of the œsophagus 35 cm. from the incisor teeth were performed. A month after admission the patient walked out of hospital able to swallow almost normal food.

Recurrent Embolism.*

Multiple or recurrent peripheral embolism should be treated in the same way as a single incident.

In mitral stenosis recurrent embolism is common (50% to 60%). Consideration of atrial appendicectomy should therefore not be delayed, because of the possibility that the next embolus may be cerebral.

Age.

Age has deliberately not been discussed in relation to the treatment of these cases because, while the likelihood of diseased arteries increases with age, it is not necessarily a contraindication to treatment. That a person is only as old as his arteries is well demonstrated by the case reported. It is the condition of the arteries that matters and not *anno Domini*.

Summary.

In recent years doubt has been cast by some people on the generally accepted surgical view that the proper treatment of peripheral arterial embolism is operative removal.

The literature bearing on this is discussed and the fallacies are pointed out.

The pathology and clinical features of the condition are reviewed and the importance of the collateral circulation in determining the natural outcome of occlusion is emphasized, and also the doubtful significance of spasm.

Based on the known facts the following scheme of management is suggested: (i) diagnosis; (ii) general measures—the relief of pain, the treatment of shock and the assessment of the patient as a whole; (iii) local measures—prevention of further damage from trauma and infection (careful nursing and antibiotics when indicated), prevention of increasing ischæmia (heparin, posture and cooling) and restoration of the circulation (heparin and operation).

Embolectomy and retrograde flush are discussed, the absolute indications being occlusions of the aortic, iliac and femoral arteries and the relative indications being occlusions of the popliteal and axillary arteries.

It is emphasized that embolectomy is a surgical emergency and early referral of patients is stressed. The operation is a relatively minor disturbance even in an ill patient. In the latter it may make all the difference to the outcome by averting massive gangrene.

The aim of treatment should be restoration of normal function. Besides removal of the embolus, distal secondary thrombus and multiple emboli should be searched for and removed. A case is reported to illustrate how this is achieved by a retrograde flush technique.

Acknowledgement.

I would like to thank Mr. Ivor Lewis, M.D., M.S., F.R.C.S., for stimulating my interest in this work and for allowing me to treat the patient reported here in one of his beds while I was working as a registrar under him in 1958.

References.

ANLYAN, WILLIAM, G., and HART, D. (1957), "Special Problems in Venous Thrombo-embolism", *Ann. Surg.*, 146: 499.

CRAWFORD, E. S., and DEBAKEY, M. E. (1956), "The Retrograde Flush Procedure in Embolectomy and Thrombectomy", *Surgery*, 40: 737.

JACOBS, A. L. (1959), Discussion on peripheral arterial disease, "Medical Aspects of Arterial Embolism", *Proc. roy. Soc. Med.*, 52: 159.

KEY, E. (1922), *Acta chir. scand.*, volume 54, quoted by Lahey, F., *loco citato*.

LAHEY, F. (1926), "The Treatment of Emboli in the Peripheral Vessels", *Surg. Clin. N. Amer.*, 6: 651.

MCGARITY, W. C., LOGAN, W. D., JUN., and COOPER, F. W. (1958), "Peripheral Arterial Embolism", *Surg. Gynec. Obstet.*, 106: 399.

MARTIN, P. (1959), Discussion on peripheral arterial disease, "Surgical Management of Arterial Embolism", *Proc. roy. Soc. Med.*, 52: 165.

MAVOR, G. E. (1958), "The Pathology and Management of Chronic Ischæmia of the Lower Limb", *J. roy. Coll. Surg. (Edin.)*, 3: 278.

OLIVIN, J H., DYE, W. S., and JULIAN, O. C. (1953), "Late Peripheral Embolectomy", *Arch. Surg.*, 66: 480.

OLOVSON, T (1941), *Acta chir. scand.*, volume 86, quoted by Jacobs, A. L., *loco citato*.

ROSS, J. P. (1944), Discussion on peripheral vascular lesions, *Proc. roy. Soc. Med.*, 37: 621.

SHAW, R. S. (1956), "A More Aggressive Approach Towards Restoration of Blood Flow in Acute Arterial Insufficiency", *Surg. Gynec. Obstet.*, 103: 279.

WARREN, R., LINTON, R. R., and SCANNELL, J. G. (1954), "Arterial Embolism, Recent Progress", *Ann. Surg.*, 140: 311-317.

Reports of Cases.

NEONATAL JAUNDICE: TWO CASES ASSOCIATED WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY IN ERYTHROCYTES.

By CHARLES LEE,
Honorary Assistant Physician,
ARNOLD TINK,
Honorary Assistant Physician,
Royal Alexandra Hospital for Children,
AND
HELEN ROBIN,
Research Assistant,
AND
JOHN HARLEY,
Research Fellow,
Children's Medical Research Foundation, Royal Alexandra Hospital for Children, Sydney.

SMITH AND VELLA in 1960 reported the occurrence of severe jaundice and kernicterus in infants born in Singapore. They found that jaundice in these infants was due to hæmolysis associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency in the red cells. They also found G6PD deficiency in two out of 76 specimens of cord blood from Chinese males. In a recent article, Doxiadis *et alii* (1961) emphasize the fact that genetically determined G6PD deficiency is an important cause of neonatal jaundice in Greek infants. In their series, one-third of full-term Greek infants with severe neonatal jaundice showed no evidence of isoimmunization; in the majority of these cases there was evidence of G6PD deficiency. These authors also mention several previous isolated reports of neonatal jaundice associated with G6PD deficiency (Newton and Bass, 1958; Zinkham and Lenhard, 1959; Shahidi and Diamond, 1959).

The object of this paper is to present two infants with G6PD deficient erythrocytes who developed anæmia and jaundice in the first four weeks of life.

Case I.

A male infant, of Italian parents, was first examined by one of us (A.R.T.) on October 14, 1960, at the age of seven months, when he was admitted to hospital with the following history. The pregnancy had been normal except for slight toxæmia, and the birth instrumental at full term. The child weighed 8 lb. 12·5 oz. at birth and sucked vigorously. His progress was uneventful except for mild jaundice on the third day of life. He was fully breast fed and remained well until the age of 23 days, when he suffered from mild diarrhœa. On the following day, March 14, he was admitted to hospital with lethargy, pallor and jaundice. The results of investigation were as follows. The hæmoglobin value was 9·3 grammes per 100 ml., the erythrocytes numbered 2,600,000 per cubic millimetre, with 2% of reticulocytes. The total serum bilirubin content was 12·1 mg. per 100 ml., and the conjugated serum bilirubin content 0·5 mg. per 100 ml. The result of the direct Coombs test was negative. The child's blood group was B, Rh(D)-positive, and the mother's blood group O, Rh(D)-positive. The child improved rapidly in hospital, and no definite diagnosis was made. Prior to onset of his jaundice his mother had been taking A.P.C. powders for headaches.

After this episode he remained well until three weeks before his second admission to hospital at the age of seven months, when he developed bronchitis, diarrhœa and fever, for which he was given chloramphenicol for four days. After this illness he improved, but took his feedings reluctantly. Two days before his admission he became very pale and passed dark urine. Slight jaundice was noted by his mother. On examination on October 14, he was very pale with slight jaundice. His nutritional state was excellent. He was active and not distressed. The tip of his spleen was palpable, but his liver did not appear enlarged. There was no bruising, and the lymph nodes were normal. No other abnormality was detected. The results of laboratory investigation were as follows. The hæmoglobin value was 6·0 grammes per 100 ml., and the erythrocytes numbered 2,000,000 per cubic millimetre; reticulocytes comprised 14% of the erythrocytes; erythroblasts numbered 1000 per cubic millimetre; numerous spherocytes were noted in a smear of peripheral blood. The results of direct and indirect Coombs tests were negative.

After his admission to hospital the child rapidly improved without blood transfusion. Six days later the hæmoglobin value was 9·0 grammes per 100 ml., erythrocytes numbered 2,600,000 per cubic millimetre, and reticulocytes comprised 4% of the erythrocytes. Two weeks after his admission the hæmoglobin value was 11·5 grammes per 100 ml. and the child seemed well. His spleen was no longer palpable.

In each parent, estimations of the hæmoglobin and fœtal hæmoglobin values and of the degrees of osmotic fragility and autohæmolysis gave results within the normal range, and no abnormality was found in a smear of peripheral blood.

In view of the child's racial origin and the presence of hæmolytic anæmia, his parents were questioned specifically about broad-bean ingestion. It was found that during the period in which he was difficult with cow's milk feedings, for two weeks prior to his admission to hospital, he was offered, and readily took, on three or four occasions, a vegetable *purée* containing fresh boiled broad beans.

Both parents came from southern Italy. The child's father and his relatives had always been healthy, but his mother was stated to have had episodes of yellowing of the eyes on four or five occasions during the first 20 years of her life.

The following special investigations were performed on the child and each parent. The G6PD activity of the erythrocytes was assayed by the method of Zinkham (1959). Methods were employed as described by Beutler (1957) for the glutathione stability test, and by Beutler *et alii* (1955) for the Heinz body incubation test. The results obtained are summarized in Table I. The G6PD activity of the erythrocytes of each parent was within the range for normal adults by the method as employed in this laboratory (110 to 180 units per 100 ml. of erythrocytes). The G6PD activity of the infant's erythrocytes was greatly decreased both during and after the episode of excessive hæmolysis.

The reduced glutathione (GSH) content of the erythrocytes before incubation with acetyl phenylhydrazine was within the normal range in each subject. After incubation, the GSH content of the erythrocytes was found to have decreased normally in the parents, but greatly in the child. After incubation for four hours with acetyl phenylhydrazine, more than 90% of the child's erythrocytes contained more than five Heinz bodies, whereas not more than 12% of the erythrocytes of either parent contained more than five Heinz bodies. The results of the Heinz body incubation test were thus normal in the parents and abnormal in the child.

Case II.

A female infant, of Greek parents, was first examined by one of us (C.L.) at the age of eight days. She was born three weeks prematurely after an otherwise normal pregnancy. She weighed 6 lb., and appeared well developed and healthy. On the first day of her life she was given an intramuscular injection of 2 mg. of an aqueous solution of a vitamin K analogue (menaphthone sodium bisulphite, which is the sodium bisulphite compound of 2-methyl-1:4-naphthoquinone). Jaundice was noticed on the third day and increased over the subsequent days. On the sixth day she became lethargic,

and feeding was difficult. When seen on the eighth day she was lethargic and very jaundiced; her urine was dark, and bile was present in the motions. Muscle tone was normal, there were no abnormal movements, and the child did not appear particularly ill. The liver and spleen were not enlarged.

There is one older child, a female, aged 12 months, who has had no significant illness. The father had an episode of acute jaundice at the age of nine or ten years after eating broad beans. He still eats these but has had no further trouble. The mother also eats broad beans, but has not done so since November, 1960, and has had no recognizable ill effects.

TABLE I.

Results of Investigation of the Erythrocytes of the Members of the Family Described in Case I.

Subject.	Units of G6PD per 100 ml. of Erythrocytes.	Milligrammes of GSH per 100 ml. of Erythrocytes.		Percentage of Erythrocytes with More than Five Heinz Bodies.
		Before Incubation.	After Incubation.	
Father ..	117	84	65	9
Mother ..	132	77	58	12
Child.. ..	7	65	15	92

The child was investigated in hospital. The hæmoglobin value was 14·6 grammes per 100 ml., the erythrocytes numbered 4,000,000 per cubic millimetre, and reticulocytes comprised less than 0·5% of the erythrocytes. Spherocytes were noted in a smear of peripheral blood. The total serum bilirubin content was 15·3 mg. per 100 ml., and the conjugated serum bilirubin content 0·6 mg. per 100 ml.

The following report was received from the Red Cross Blood Transfusion Service. The mother's blood group was B, Rh (D)-positive, the baby's blood group was B, Rh (D)-positive. No antibodies were detected in the mother's serum against the baby's red blood cells by the polyvinylpyrolidone (PVP) and indirect Coombs tests.

The jaundice gradually lessened, and the total serum bilirubin content on the seventeenth day was 5·5 mg. per 100 ml. The child took breast feeding well and was discharged from hospital.

The results of special investigations on the erythrocytes of the patient and her parents are shown in Table II. These investigations were performed on the child at the age of 11 days, three days after her admission to hospital, at the stage when jaundice was still present, but subsiding. The G6PD activity of the erythrocytes was normal in the mother and much decreased in the father. The G6PD activity of the infant's erythrocytes was well below the range of normal new-born infants, which is 215 to 410 units per 100 ml. of erythrocytes (Zinkham, 1959). The results of the glutathione stability test and Heinz body incubation test were normal in the mother and very abnormal in the father. The infant's erythrocytes yielded a positive result to the Heinz body incubation test, but reacted normally to the glutathione stability test.

Discussion.

The genetically determined metabolic defect commonly present in people of Mediterranean origin, and other racial groups as yet incompletely defined, which explains their susceptibility to hæmolytic anæmia on exposure to *Vicia faba*, phenacetin, primaquine, sulphonamide and other substances, has been adequately considered in the literature of recent years. Erythrocytes from such sensitive people have been shown to be unduly susceptible to Heinz body production when incubated with acetyl phenylhydrazine (Beutler *et alii*, 1955), unable to protect their reduced GSH from oxidation when incubated with acetyl phenylhydrazine (Beutler, 1957), and deficient in the enzyme G6PD (Carson *et alii*, 1956).

The relationship between erythrocyte G6PD deficiency and neonatal jaundice has only recently been emphasized (Smith and Vella, 1960; Doxiadis *et alii*, 1961). To our knowledge, this relationship has not previously been reported in the Australian medical literature. Each of the two infants presented developed jaundice during the first month of life. The history of the child in Case I suggests the possibility of exposure to phenacetin or acetylsalicyclic acid in the breast milk of the mother. Both drugs may produce hæmolytic anæmia in sensitive subjects (de Gruchy, 1960), and acetylsalicyclic acid is known to be excreted in breast milk (Goodman and Gilman, 1955). Subsequently, at the age of seven months, this infant developed acute hæmolysis after ingestion of the common broad bean, *Vicia faba*. Less closely related to this second episode was the ingestion of chloramphenicol, which may also produce hæmolysis in susceptible individuals (Larizza, *et alii*, 1960). Possibly one or both of these episodes of anæmia and jaundice resulted from the combined effect of multiple hæmolytic agents.

The infant in Case II developed jaundice after the injection of 2 mg. of a vitamin K analogue. The relationship between the administration of certain vitamin K analogues and kernicterus is well established (Allison, 1955). Although no precipitating factors were found in more than half the new-born infants described by Doxiadis *et alii* (1961), it is of some interest that 15 of the 82 full-term infants with severe jaundice without evidence of isoimmunization had received 1 to 5 mg. of a vitamin K analogue; 12 of these 15 infants were admitted to hospital with kernicterus. Vitamin K analogues have been shown to act directly on the erythrocyte both *in vitro* and *in vivo* to cause methæmoglobin formation and oxyhæmoglobin destruction (Harley and Mauer, 1960), *in vitro* to cause Heinz body production (Harley and Mauer, 1961), and *in vivo* to cause massive hæmolysis and hæmoglobinuria (Zbinden, *et alii*, 1957). The ability of some vitamin K analogues to oxidize intraerythrocytic GSH is such that certain of these compounds have been substituted for acetyl phenylhydrazine in the glutathione stability test for sensitive erythrocytes (Zinkham, 1959). Glucose-6-phosphate dehydrogenase deficiency would thus be expected to render the erythrocytes more susceptible to the hæmolytic effect of the vitamin K, so that a smaller dose would produce greater hæmolysis *in vivo*. The administration of the vitamin K analogue may thus have been a significant factor in the development of severe neonatal jaundice in the second infant.

TABLE II.

Results of Investigation of the Erythrocytes of the Members of the Family Described in Case II.

Subjecr.	Units of G6PD per 100 ml. of Erythrocytes.	Milligrammes of GSH per 100 ml. of Erythrocytes.		Percentage of Erythrocytes with More than Five Heinz Bodies.
		Before Incubation.	After Incubation.	
Father ..	12	40	8	92
Mother ..	119	87	83	22
Child.. ..	93	60	55	93

Pronounced G6PD deficiency, GSH instability and susceptibility to Heinz body formation were found in the erythrocytes of the infant described in Case I. The failure to detect evidence of abnormality in the erythrocytes of this child's parents deserves comment, as G6PD deficiency, GSH instability or both are usually found in at least one parent of a sensitive subject. In this and certain other families, no abnormality has been detected in either parent (Naylor, *et alii*, 1960). A possible explanation suggested by Childs *et alii* (1958) is that the mode of inheritance of sensitive erythrocytes is sex-linked with variable expressivity, so that a heterozygous female with minimal signs of sensitivity

may transmit the defect to a frankly sensitive hemizygous male.

The biochemical and genetic aspects of the studies on the erythrocytes of the family in Case II are also of interest. The investigations indicate that the erythrocytes of the father are frankly sensitive, whereas those of the mother are normal. The G6PD activity of the infant's erythrocytes, while only slightly less than the normal adult range, was well below the range for normal new-born infants. The normal result of the glutathione stability test in the infant may be related to the transient loss of GSH instability reported as following drug-induced hæmolysis (Szeinberg *et alii*, 1958; Dawson *et alii*, 1958). Erythrocytes from normal neonates are known to be unduly prone to form Heinz bodies when exposed to oxidants (Brown, unpublished), so that the positive result of the Heinz body incubation test is not necessarily significant in this new-born infant. However, the demonstration of a relative G6PD deficiency in this genetically heterozygous female infant strongly suggests the presence of a metabolic defect in the infant's erythrocytes.

The occurrence of favism in breast-fed infants has been known for many years. This has been referred to by Preti (1927), by Casper and Shulman (1956), and more recently by Emanuel and Schoenfeld (1961), who report the occurrence of hæmolytic anæmia in a breast-fed female, aged four months, three days after the mother had eaten fava beans. The parents of this child were Oriental Jews. To our knowledge, neither of the mothers of our children ate broad beans at the time when the children became ill. However, the acute hæmolytic anæmia which followed ingestion of *Vicia faba* by the patient in Case I emphasizes the increasing importance of favism in Australia, and serves to draw attention to the common broad bean, which is, in fact, *Vicia faba* (Figure I).

In 1948, Rosen and Scanlan, discussing the American case reports of favism since 1933, wrote:

> It is the purpose of this report . . . to call attention to the fact that the fava bean (broad bean), in addition to being imported, is now being grown in this country. It appears very probable that many more cases would be discovered here if this entity were considered in the differential diagnosis of acute hæmolytic anæmia.

More cases of favism are known in Australia than those now described in detail (Harley and Dods, 1957, 1959; Brooks *et alii*, 1958; Moore, 1958; McCutcheon, 1960). De Gruchy (1960) mentioned several unreported cases, and we are aware of two additional children with acute hæmolytic anæmia following exposure to *Vicia faba*. The relative frequency of this disease may be related, not only to the influx of Mediterranean and other susceptible people, but also to the favourable effect of the Australian coastal climate on the cultivation of the broad bean.

Favism is definitely seasonal, most cases occurring in spring, when the beans are fresh and pollen of the blossoms is in the air. Most of the episodes of excessive hæmolysis in patients with favism known to us or described in the Australian literature, including the first subject of the present report, have occurred during the months of October or November. Noteworthy, however, is the excessive hæmolysis which may result in such patients at other times of the year, from exposure to dried broad beans or other known hæmolytic agents. To persons with sensitive erythrocytes, the fresh broad bean is thus a seasonal hazard against a background of susceptibility to the hæmolytic effect of many other chemical and vegetable substances.

The rapid recovery of both children without blood transfusion is consistent with the observation of Dern *et alii* (1954), that approximately half of the population of sensitive erythrocytes is destroyed after the ingestion of primaquine. As recently as 1956, however, Crosby reported that 40 to 50 deaths from favism occurred annually on the island of Sardinia, that the disease was more common in children, and that those who died were usually less than six years old. He also reported that early and adequate transfusion produced an almost miraculous transformation in children moribund with circulatory shock and anæmia. Casper and Shulman (1956) reported death with bilateral renal cortical necrosis in an infant with favism. While blood transfusion may often be unnecessary, these observations emphasize the serious nature of drug-induced hæmolysis and the importance of critical assessment of the child throughout the episode of excessive hæmolysis.

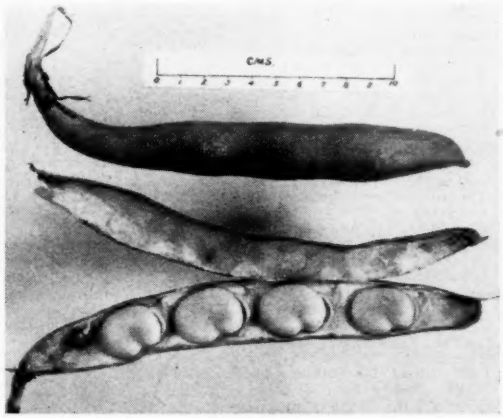

FIGURE I.
The broad bean, *Vicia faba*.

Simple blood transfusion may not represent adequate therapy in the neonatal period, as severe jaundice may cause kernicterus and death before the hæmoglobin level falls very low (Smith and Vella, 1960). The importance of an awareness of this syndrome of neonatal jaundice due to G6PD deficiency has been emphasized by Doxiadis *et alii* (1961), who stress the need for close observation of the serum bilirubin levels and for exchange transfusion when dangerous levels are reached. These authors also recommend that in racial groups in which G6PD deficiency is prevalent, the use of vitamin K analogues in both expectant mother and new-born infant should be limited as strictly as possible, and that particular attention should be paid to families with a history of a previously affected infant, of favism or of drug-induced hæmolysis. These considerations would appear to represent a rational basis for the prevention and management of severe jaundice and its complications in the new-born infants of certain susceptible racial groups.

Summary.

The histories of two infants with G6PD deficient erythrocytes have been described. Both were of Mediterranean descent, and both developed jaundice in the first month of life.

The first child's episode of anæmia and jaundice at the age of three weeks may have been related to the presence of phenacetin and acetylsalicyclic acid in his mother's breast milk. The second episode at the age of eight months was closely related to his ingestion of the common broad bean, and less closely related to his ingestion of chloramphenicol.

The second child became jaundiced at the age of three days, after the injection of 2 mg. of a vitamin K analogue.

The significance of G6PD deficiency and exposure to certain chemical and vegetable agents has been discussed in relation to neonatal jaundice and acute hæmolytic anæmia in children of appropriate racial extraction.

Reference is made to the probable frequency of the condition in this country, and to the need to protect susceptible new-born infants and older children from various chemical hazards which may produce massive hæmolysis of the affected red cells.

Acknowledgements.

We should like to thank Dr. T. Penna and Dr. R. D. Danesi for referring these patients.

References.

ALLISON, A. C. (1955), "Danger of Vitamin K to Newborn", *Lancet*, 1: 669.

BEUTLER, E., DERN, R. J., and ALVING, A. S. (1955), "The Hemolytic Effect of Primaquine. VI. An In Vitro Test for Sensitivity of Erythrocytes to Primaquine", *J. Lab. clin. Med.*, 45: 40.

BEUTLER, E. (1957), "The Glutathione Instability of Drug-Sensitive Red Cells. A New Method for the In Vitro Detection of Drug Sensitivity", *J. Lab. clin. Med.*, 49: 84.

BROOKS, E. A. V., JAMES, G. A., and STUBBER, L. A. (1958), "Favism in Western Australia", MED. J. AUST., 2: 455.

BROWN, A. K., "Peculiarities of Erythrocytes of the Newborn", Transactions of the Panel on Kernicterus, 9th International Congress of Pediatrics, Montreal, Canada, July, 1959 (to be published).

CARSON, P. E., FLANAGAN, C. L., ICKES, C. E., and ALVING, A. S. (1956), "Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes", *Science*, 124: 484.

CASPER, J., and SHULMAN, J. (1956), "Bilateral Cortical Necrosis of the Kidneys in an Infant with Favism", *Amer. J. clin. Path.*, 26: 42.

CHILDS, B., ZINKHAM, W., BROWNE, E. A., KIMBRO, E. L., and TORBERT, J. V. (1958), "A Genetic Study of a Defect in Glutathione Metabolism of the Erythrocytes", *Bull. Johns Hopk. Hosp.*, 102: 21.

CROSBY, W. H. (1956), "Favism in Sardinia", *Blood*, 11: 91.

DAWSON, J. P., THAYER, W. W., and DESFORGES, J. F. (1958), "Acute Hemolytic Anemia in the Newborn Infant due to Naphthalene Poisoning: Report of Two Cases, with Investigations into the Mechanism of the Disease", *Blood*, 13: 1113.

DE GRUCHY, G. C. (1960), "Red Cell Metabolism: Fundamental and Clinical Aspects", *Aust. Ann. Med.*, 9: 237.

DERN, R. J., BEUTLER, E., and ALVING, A. S. (1954), "The Hemolytic Effect of Primaquine. II. The Natural Course of the Hemolytic Anemia and the Mechanism of its Self-Limited Character", *J. Lab. clin. Med.*, 44: 171.

DOXIADIS, S. A., FESSAS, P., VALAES, T., and MASTROKALOS, N. (1961), "Glucose-6-Phosphate Dehydrogenase Deficiency. A New Ætiological Factor of Severe Neonatal Jaundice", *Lancet*, 1: 297.

EMANUEL, B., and SCHOENFELD, A. (1961), "Favism in a Nursing Infant", *J. Pediat.*, 58: 263.

GOODMAN, L. S., and GILMAN, A. (1955), "The Pharmacological Basis of Therapeutics", 2nd Edition, Macmillan, New York.

HARLEY, J. D., and DODS, L. (1957), "Hæmolysis following the Ingestion of Uncooked Broad Beans", MED. J. AUST., 2: 561.

HARLEY, J., and DODS, L. (1959), "Some Acquired Hæmolytic Anæmias of Childhood", *Aust. Ann. Med.*, 8: 98.

HARLEY, J. D., and MAUER, A. M. (1960), "Studies on the Formation of Heinz Bodies. I. Methemoglobin Production and Oxyhemoglobin Destruction", *Blood*, 16: 1722.

HARLEY, J. D., and MAUER, A. M. (1961), "Studies on the Formation of Heinz Bodies. II. The Nature and Significance of Heinz Bodies", *Blood*, 17: 418.

LARIZZA, P., BRUNETTI, P., and GRIGNANI, F. (1960), "Enzyme-Deficiency Hæmolytic Anæmias", *Lancet*, 1: 601.

LARKIN, V. DE P. (1953), "Favism: Report of a Case and a Brief Review of the Literature", *J. Pediat.*, 42: 453.

MCCUTCHEON, A. D. (1960), "Drug-Induced Hæmolytic Anæmia and Favism", MED. J. AUST., 2: 561.

MOORE, H. S. (1958), "A Suspected Case of Favism", MED. J. AUST., 2: 733.

NAYLOR, J., ROSENTHAL, I., GROSSMAN, A., SCHULMAN, I., and HSIA, D. Y. (1960), "Activity of Glucose-6-Phosphate Dehydrogenase in Erythrocytes of Patients with Various Abnormal Hemoglobins", *Pediatrics*, 26: 285.

NEWTON, W. A., JUN., and BASS, J. C. (1958), "Glutathione-Sensitive Chronic Nonspherocytic Hemolytic Anemia", *Amer. J. Dis. Child.*, 96: 501.

PRETI, L. (1927), *"Ueber den sogenannten 'Fabismus'"*, *Klin. Wschr.*, 6: 2429; quoted by Larkin, *loco citato*.

ROSEN, A. P., and SCANLON, J. J. (1948), "Favism", *New Engl. J. Med.*, 239: 367.

SHAHIDI, N. T., and DIAMOND, L. K. (1959), "Enzyme Deficiency in Erythrocytes in Congenital Non-Spherocytic Hæmolytic Anæmia", *Pediatrics*, 24: 245.

SMITH, G. D., and VELLA, F. (1960), "Erythrocyte Enzyme Deficiency in Unexplained Kernicterus", *Lancet*, 1: 1133.

SZEINBERG, A., ASHER, Y., and SHEBA, C. (1958), "Studies on Glutathione Stability in Erythrocytes of Cases with Past History of Favism or Sulfa-Drug-Induced Hemolysis", *Blood*, 13: 348.

ZBINDEN, G., SCHÄROR, K., and STUDER, A. (1957), *"Experimentelle Untersuchungen über Erythrocytenschädigung durch Menadionderivate im Vergleich zu Vitamin K_1"*, *Schweiz. med. Wschr.*, 87: 1238.

ZINKHAM, W. H. (1959), "An In-Vitro Abnormality of Glutathione Metabolism in Erythrocytes from Normal Newborns: Mechanism and Clinical Significance", *Pediatrics*, 23: 18.

ZINKHAM, W. H., and LENHARD, R. E., JUN. (1959), "Metabolic Abnormalities of Erythrocytes from Patients with Congenital Nonsperocytic Hemolytic Anemia", *J. Pediat.*, 55: 319.

GYNÆCOMASTIA AND MULTIPLE MYELOMA.

By J. E. GAULT, M.R.A.C.P.,

From the Repatriation General Hospital, Heidelberg.

GYNÆCOMASTIA is a not uncommon condition which has been associated with many diseases, but it is believed that an association with multiple myeloma has not previously been described.

Clinical Record.

A retired man, aged 68 years, had had a chronic psychoneurosis for years, and his history was hard to obtain as he was hypomanic and garrulous. His chief complaint was of four months' vague abdominal pain, commencing about June or July, 1960. Its site varied at each description, and it was associated with anorexia, distension and constipation. It did not appear to be characteristic of ulcer pain, colic (bowel or renal) or nerve-root pain. At about the same time he developed painful swellings of both breasts, over a period of a week or two, and although the breasts were still large the pain had decreased. He had angina pectoris and dyspnœa on exertion, which was related to chronic bronchitis. He had not been taking digitalis or other drugs. A simple cyst of the right kidney had been removed in October, 1959, the pre-operative diagnosis having been made of neoplasm. His sexual urge had been absent for four years, and he only occasionally partook of alcohol.

On examination he was seen to be moderately obese, with sparse axillary and pubic hair, and his testicles were diminished in size. Painful, enlarged breast tissue could be felt and distinguished from the overlying fat (Figure I). The bruit of aortic sclerosis was noted. He did not appear myxœdematous; he was not hypertensive, and there were no signs of heart failure.

Investigations revealed a normochronic anæmia, with a hæmoglobin level of 11·6 grammes per 100 ml., a white-cell count of 6200 with a normal differential count, and an erythrocyte sedimentation rate of 76 mm. in the first hour (Westergren). The results of liver function tests were as follows: The serum albumin level was 3·0 grammes per 100 ml.; the serum globulin level was 5·9 grammes per 100 ml.; the serum-alkaline phosphatase level was 8 King-Armstrong units; the serum bilirubin level was less than 0·2 mg. per 100 ml. and the cephalin flocculation test gave a negative result. Radiographic examination of the skull showed a number of round translucencies characteristic of myeloma, and serum electrophoresis showed a characteristic pattern, with a prominent band between the beta and gamma globulin fractions (Figure II). A trace of Bence-Jones protein was found in the urine, and urine electrophoresis disclosed a similar pattern. Bone-marrow biopsy showed a non-specific plasmocytosis consistent with, but not diagnostic of, myeloma. The serum calcium level was 12·0 mg. per 100 ml. and the serum phosphorus level was 4·0 mg. per 100 ml.

Radiographic examination of the chest, a cholecystogram, an electrocardiogram and the "Bromsulphalein" retention were all normal. The levels of the serum acid phosphatase, urinary diastase and serum transaminase were within normal limits. A Sia test gave a negative result. Radiographic examination of the lumbar spine showed generalized osteoporosis, while renal function tests showed a fasting blood-urea level of 58 mg. per 100 ml. and a urea clearance of 56%; a concentration of 2·64% of urea was reached and urea excretion was 6·3 grammes in three hours.

The normal "Bromsulphalein" retention, serum transaminase level and liver function test results exclude significant liver disease. Presumably he had some mild renal damage, but, although chronic pyelonephritis and glomerulonephritis are mentioned as causes of gynæcomastia, the renal damage was slight, whereas in these conditions it is associated with moderate or severe uræmia. A renal tumour had previously been excluded. He was not a diabetic, and there were no signs of endocrine disorders such as thyrotoxicosis, myxœdema, acromegaly or Cushing's syndrome. His nutrition was good,

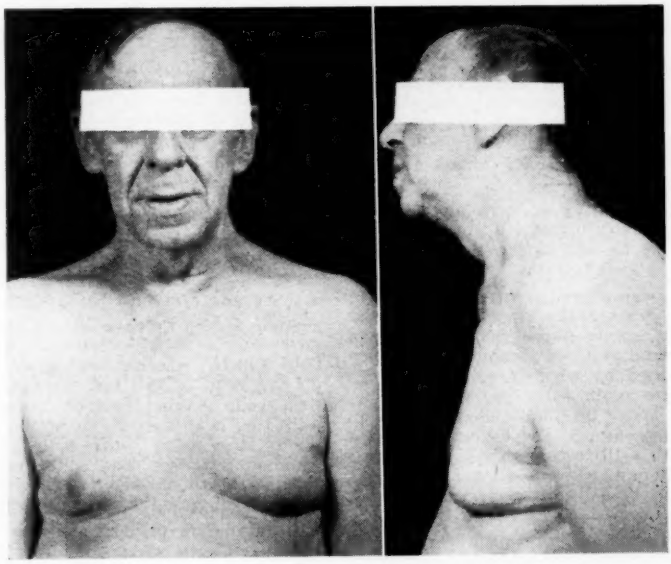

FIGURE I.

The patient's symptoms were not severe enough to warrant specific therapy for myelomatosis, and he was discharged with symptomatic treatment only.

Discussion.

It is hard to say when the commencement of myelomatosis occurred, and because of the lack of an agent

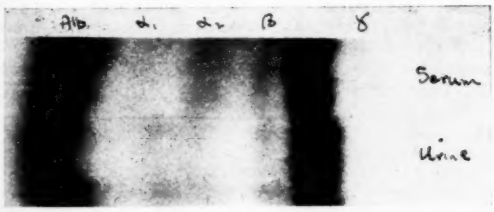

FIGURE II.

which could completely reverse the myelomatous process, one cannot prove the association between multiple myeloma and gynæcomastia in this case. However, by a process of exclusion, it seems reasonable to associate the two.

Senile testicular atrophy with hypogonadism had been present for at least four years, and the development of gynæcomastia in this condition is gradual and usually painless, being related in time to the occurrence of the senile change. However, one cannot exclude this entirely as being the cause of the gynæcomastia. There was no suggestion of testicular tumour or inflammation.

he was not hypertensive, he did not have heart failure and his prostate was only moderately hypertrophied. There was no reason to suspect bronchial carcinoma.

Apart from the hormonal relationships in testicular and other endocrine diseases, and in liver disease, the ætological relationship of gynæcomastia to the other conditions mentioned above, and to many other diseases, is hard to understand, and may even be coincidental. However, a useful working rule quoted by Wheeler and his associates is: "Gynæcomastia beginning before the age of 25 is usually a manifestation of puberty. After the age of 25 it is usually a manifestation of serious underlying disease." The case illustrated provides an example of the truth of this dictum.

Summary.

A case is described in which gynæcomastia commenced four months before a diagnosis of multiple myeloma was made, and by a process of exclusion it is suggested that the two may be related.

Acknowledgements.

I wish to think the Chairman of the Repatriation Commission for permission to publish this case, Dr. John Owen of St. Vincent's Hospital for performing the urine electrophoresis and Dr. F. Catarinich for his helpful discussion.

References.

HALL, P. F. (1959), "Gynæcomastia", Australasian Medical Publishing Company, Sydney.

TREVES, N. (1958), "Gynæcomastia — the Origin of Mammary Swellings in the Male", *Cancer (Philad.)*, 11: 1083.

WHEELER, C. E., CAWLEY, E. P., GRAY, H. T., and CURTIS, A. C. (1954), "Gynæcomastia; Review and Analysis of 160 Cases", *Ann. intern. Med.*, 40: 985.

CASE OF MILK ALLERGY.

By HELEN B. WILES, M.B., B.S., D.C.H.,
Canberra.

AMONG the feeding problems of infancy, milk allergy is relatively rarely diagnosed. Nevertheless, in some instances it is unmistakable and severe, and from the classic form there appear to be varying gradations of severity.

The following is the case of a male infant with a severe allergic diathesis manifested first as cow's milk allergy.

Clinical Record.

The patient's paternal grandfather suffered from bronchial asthma, and his mother and father are prone to hay fever. His younger brother suffers from asthma. There is no family history of milk allergy. During the pregnancy the mother, who disliked cow's milk, took large quantities of cheese as a substitute.

The patient, a male, was healthy at birth and of birth weight 7 lb. 1 oz. He was fully breast fed until 18 weeks of age. During this period he was said to be "cross and colicky", but made average weight gains.

At 18 weeks of age he was offered a wheat cereal with a little cow's milk. He refused the cereal, vomited the little forced on him and rapidly developed a widespread urticarial rash. On the same day he had upper respiratory tract symptoms accompanied by wheezing. At 22 weeks the same meal was offered, again with the same reaction. The Baby Health Clinic sister attributed the reaction to an allergy to wheat, and so oatmeal and barley were tried in turn instead, each with a little cow's milk. The same reaction followed each attempt. On one of these occasions a little cow's milk spilt on the baby's face caused a "burn".

At 24 weeks a complement was becoming necessary, owing to a deficiency of breast milk, and sweetened condensed milk (a one-in-eight mixture) was offered. Vomiting, rash and wheezing were immediate effects. Then wheat cereal was offered with water instead of milk, and was taken well and without reaction. Thus cow's milk was inculpated as the cause. A milk substitute derived from soya bean flour was then offered and taken without ill effects, and vegetables and meat broth were then added to the baby's diet.

Goat's milk, a dried full-cream powdered milk and an evaporated (unsweetened, condensed) milk were tried in turn at intervals, each without success, and henceforth the soya bean milk was continued.

In the ensuing months the baby was found to refuse egg and to vomit it if it was forced, so it was likewise avoided.

At six months of age the baby developed an attack of croup which proceeded to bronchial asthma, and the same occurred at seven months. From then onwards asthma attacks of variable severity and attacks of "nervous vomiting" became troublesome. Asthma appeared to be precipitated by psychological upsets, upper respiratory tract infections and the surreptitious swallowing of milk chocolate. However, by now small amounts of milk were tolerated in cake.

Vomiting and the refusal of all types of food became troublesome as part of a general behaviour problem in the second year. From the time of weaning the child's weight had remained below average. At 20 months he commenced to gain normally.

At the age of two years and three months the child had two hæmatemeses and was admitted to hospital. Plain X-ray films of the chest and the abdomen and subsequent barium-swallow and barium-meal studies showed no abnormalities. In hospital he inadvertently received some raw cow's milk and developed status asthmaticus, which lasted for 24 hours.

At the age of two years and nine months allergy skin-testing showed a sensitivity to milk, egg and wheat flour.

After each of his triple antigen injections (at two years and eight months of age) he was unwell and had mild asthma for two days. Asthmatic attacks have dogged his course since, but have become sparser and milder, and now, at the age of three years and eight months, he appears physically and psychologically robust.

A course of desensitization to cow's milk was begun at the age of three years and six months by giving him minute quantities greatly diluted in water in gradually increasing amounts. It has been necessary to proceed very slowly to avoid wheezing.

Discussion.

As mentioned above, milk allergy in the human infant varies with regard to the severity and the symptomatology, and also to the types of milk which provoke reactions. Rarely, anaphylactic shock may be manifested even at a first feeding of breast milk. The cyanosis provoked is frequently then attributed to other causes related to the mechanics of feeding. It is thought that sensitization has here occurred by placental transfer *in utero*.

Less acute symptoms of urticarial rash, asthma, vomiting, colic and diarrhœa may be provoked and incomplete forms occur. Less acutely still it may be manifested by a low-grade diarrhœa or infantile eczema.

Some babies are allergic to all milks, including human milk, while others tolerate human milk exclusively. Others have a specific cow's milk allergy but may be reared on the milk of another mammal—for example, the goat. One group is comprised of babies who react to raw cow's milk, but who tolerate it when boiled—this is less commonly seen today, when boiling cow's milk for babies is common practice. The commonest group today probably consists of those who are allergic to cow's milk, except in the evaporated form (unsweetened condensed).

A distinction may be made as to the particular protein in the milk to which the baby is allergic—that is, lactalbumin, lactoglobulin or casein. In clinical experience in the past the whey proteins have been held the most allergenic. Ratner *et alii*, in experiments on guinea-pigs, produced anaphylaxis in the intact animal and measured spasm in isolated guinea-pig intestine with pure preparations of specific milk proteins (Ratner *et alii*, 1958). They found beta lactoglobulin the most allergenic and alpha lactalbumin and alpha casein to have definite, but less potent, allergenicity. Comparing challenge by the oral route in guinea-pigs between commercial preparations of heat-denatured milk (evaporated—that is, unsweetened and condensed) and pasteurized milk, they found the latter of much higher allergenicity than the former (Ratner *et alii*, 1958).

This would conform with the clinical finding in human infants that milk allergy is most commonly not manifested to evaporated milk, since in the processing it is heated sufficiently to denature the beta lactoglobulin and the alpha lactalbumin. Sweetened condensed milk is not so treated. However, the rarer form of allergy to casein, which is relatively heat stable, may be manifested by allergy to "milk in any form" and for this a milk substitute is necessary.

The lactalbumin is species-specific as distinct from the casein, which is common to most of the milks. This explains the usual tolerance to goat's milk in babies allergic to cow's milk when lactalbumin is responsible. However, those allergic to casein can be expected to be intolerant of goat's milk as well as cow's milk.

Soya bean preparations have been the mainstay in early nutrition of those allergic to "milk in any form". Home-made preparations without additives are not ideal substitutes. They are relatively deficient in vitamin A and methionine. They themselves often provoke gastro-intestinal upsets, especially diarrhœa. However, proprietary preparations may be obtained which are usually

satisfactory. Actual allergy to soya bean is rarely acquired. Early mixed feeding is advised to allow adequate nutrition. Many of these children show multiple food allergies and each addition should be made singly.

Fortunately the sensitivity to milk is frequently lost and milk should therefore be tried again in small amounts at about 10 months of age. In the more severe cases desensitization can be safely attempted only by offering daily very minute, but gradually increasing, quantities of cow's milk.

Summary.

1. A case of severe milk allergy in a male infant is described.

2. The different clinical forms of milk allergy which may occur in infancy are discussed and the different responsible allergens compared.

3. The limitations of substitute feedings are mentioned and interim further trials of cow's milk or, in severe cases, desensitization, are recommended.

Acknowledgements.

My thanks are due to Dr. Alan G. Cumpston for permission to publish this case, and to Dr. Kate Campbell for her very helpful advice and criticism.

References.

RATNER, B., DWORETSKY, M., OGURI, S., and ASCHEIM, L. (1958), "Studies on the Allergenicity of Cow's Milk I", *Pediatrics*, 22: 445.

RATNER, B., DWORETSKY, M., OGURI, S., and ASCHEIM, L. (1958), "Studies on the Allergenicity of Cow's Milk III", *Pediatrics*, 22: 653.

NOCARDIOSIS: REPORT OF A CASE RESEMBLING SPOROTRICHOSIS.

By A. BAUMGARTEN,

Senior Resident Medical Officer, Medical Professorial Unit, Royal Adelaide Hospital, Adelaide.

NOCARDIOSIS in man was first described in 1890 by Eppinger under the title of "pseudo-tuberculosis". He demonstrated that it was an infection by *Cladothrix asteroides* as the organism was then called. The condition is becoming more frequently recognized, and several reviews have appeared, the most recent by Ballenger and Goldring (1957), who reviewed 95 cases.

Infection may become manifest in several well-defined clinical forms (Conant *et alii*, 1954). By far the commonest is the pulmonary type, with or without generalized spread. Localized infection of an extremity is less common, with the exception of "madura foot", which occurs in certain tropical areas. A rare form is cervico-facial nocardiosis, which is usually accompanied by involvement of the regional lymph glands. All forms are characterized by abscess formation, and blood-borne spread may follow.

Only three cases of human infection have been reported previously from Australia (Goldsworthy, 1937; O'Reilly and Powell, 1953; Smith and Benecke, 1960), although there have been a number of cases of infection in dogs and marsupials (Johnston, 1954; Tucker and Millar, 1953). Pulmonary lesions were present in all three of these cases. In one instance there was also cerebral involvement. All were fatal.

The present case is notable for the localized nature of the primary lesion, which involved only the superficial layers of the skin of a hand. Furthermore, secondary nodules occurred along the subcutaneous lymphatics of the arm without involvement of the regional lymph nodes. This appearance is typical of sporotrichosis, a form of presentation reported only once previously (Guy, 1920). Finally, early bacteriological diagnosis permitted prompt treatment with satisfactory results.

Clinical Record.

A male clerk, aged 30 years, was admitted to hospital on June 30, 1960. He lived in a semi-rural area on the outskirts of Adelaide, and previously had been in good health. He had no unusual living or dietary habits. Eight weeks prior to his admission, whilst he was chopping wood, a splinter entered the right hand between the heads of the second and third metacarpals. He received no treatment at that time, but on the following day the area was bathed with an antiseptic lotion and bandaged. A fortnight later the site of the puncture was visible, but there was no surrounding inflammation. Two weeks before his admission, the patient had noticed that a small amount of pus was exuding from the sinus and that the surrounding area was inflamed. A few days later superficial ulceration and encrustation appeared around the opening, and above it, over the base of the second metacarpal, there appeared a small subcutaneous nodule with reddening of the overlying skin. At this stage chlortetracycline and later chloramphenicol were given by the local practitioner. Despite this therapy, both lesions continued to enlarge, and further nodules appeared along the dorsum of the right forearm.

A swab of the ulcer was taken by the patient's practitioner on June 24, but no organisms were seen in the smear, and no growth was obtained on culture on blood agar. As the lesions continued to enlarge, the patient was referred to the Institute of Medical and Veterinary Science, Adelaide, where a sample of pus was obtained on June 29. On this occasion the smear showed an organism resembling *Nocardia asteroides*, and the patient was referred to the Medical Professorial Unit.

Examination of the patient showed him to be a well-built (183 lb.) man, who was ambulant and not obviously ill. His temperature was 98·4° F. and there was no tachycardia. On the dorsum of the right hand, between the second and third metacarpals, there was a non-tender superficial ulcer 2 cm. in diameter. The edge was irregular, the floor encrusted and the base thickened but not fixed. There were mild surrounding erythema and œdema. When some encrustations were removed, a small sinus became visible. It was possible to express a bead of pus by pressure on the surrounding tissues. The pus was yellowish, thick and of uniform consistency, and contained no granules. Proximal to the ulcer and overlying the base of the second metacarpal, there was an ovoid reddish nodule measuring 1·5 by 1·0 cm. It was fluctuant, but neither tender no translucent. It was attached to the skin, but not to the underlying tissues. It was regular and smooth in contour. Along the radial border of the dorsum of the forearm a further eight nodules were palpable. They varied in size, but none exceeded 1 cm. in diameter. Only the uppermost two were also visible. None was ulcerated or tender. The epitrochlear and axillary glands were impalpable. The skin and lymph glands of other regions were normal, and general examination of the patient revealed no other significant abnormality.

A confident clinical diagnosis of sporotrichosis was made by a number of observers. The mode of onset of the infection and its subsequent subcutaneous lymphangiitic spread were considered typical of that condition.

On the patient's admission to hospital, an X-ray examination of the chest revealed no abnormality. The hæmoglobin value was 16·1 grammes per 100 ml. and the white cell count was 7600 per cubic millimetre, the differential distribution being normal. Smears and cultures on a variety of media, including blood agar and Sabouraud's medium, were prepared on June 30, July 2 and July 4. The largest nodule was aspirated with sterile precautions on July 6. On each occasion *N. asteroides* was found both in the smears and on culture. No other pathogenic organisms were detected.

On the patient's admission, treatment was commenced with erythromycin and triple sulphonamides in a divided dosage of 3 grammes per day of each. Two days later, there appeared to be no change in the appearance of the

lesions. At this stage, 0·6 ml. of saturated potassium iodide solution was given every four hours. Two days after this, the inflammatory reaction around the ulcer had subsided and the nodular lesions had decreased a little in size. The dosage of iodide solution was increased to 5·4 ml. per day, and the improvement continued. On the sixth day, the largest nodule on the back of the hand was aspirated and the yellow pus obtained was cultured. After this procedure, there was an increase in the inflammatory reaction around the nodule, but the site of puncture closed spontaneously and did not discharge at any stage. The other nodules continued to diminish in size without interruption.

Twelve days after his admission to hospital, the patient was discharged, taking triple sulphonamides (2 grammes daily) and potassium iodide solution (5·4 ml. daily) in divided doses. At this stage, the ulcerated area had become epithelialized and the nodules had regressed to less than half their original size.

The patient was examined at frequent intervals over the next two months, during which time there was no further regression in the size of the nodules. The largest nodule on the dorsum of the hand remained fluctuant. In view of the possible danger of breakdown in this lesion when therapy was stopped, a limited block resection of the skin and subcutaneous tissue of the right hand was performed by Mr. B. N. Catchpole on September 1, 1960. The area of the primary lesion, the fluctuant nodule and two adjacent smaller nodules were removed *en bloc* and the area was covered with a split-skin graft. The few small nodules remaining along the radial border of the forearm were left intact. The grafted area healed satisfactorily. A nodule was examined microscopically by Dr. R. T. W. Reid, who reported as follows:

> The section shows the major lesion is a granuloma sited in the deeper layers of the dermis as well as in fatty tissue. It shows encapsulation, but with several small satellite non-caseating tubercles at the periphery. No nocardial elements were seen.

Discussion.

N. asteroides is allied to the genus *Actinomyces*, but differs in being aerobic. It may be cultured on any of the common media, and the colonies appear in seven to 14 days. Staining with hæmatoxylin and eosin does not occur; hence the organism may be missed on histological examination of affected tissues. An important feature is its resistance to decolorization by acid, and this may be so pronounced as to lead to confusion with *Mycobacterium tuberculosis*.

As has been stated, infection of an extremity in nocardiosis is uncommon. When this occurs, however, it is occasionally secondary to hæmatogenous spread from other sites, chiefly the lungs, but usually it follows the entry of the organism through a break in the skin (Buchanan *et alii*, 1948; Baker, 1957; Cullen and Sharp, 1951). Subsequently, an abscess forms which tends to extend into the deeper tissues, and later discharges through a complex system of sinuses. The regional lymph glands may become affected, and eventually hæmatogenous dissemination may follow.

In the present case the condition remained localized; there was no evidence of deep abscess formation, pulmonary involvement or hæmatogenous dissemination. It may be that the prompt institution of therapy arrested the spread at an early stage. As it was, the clinical features in this case closely resembled sporotrichosis, except that the primary lesion here was an indurated ulcer and not a nodule. The repeated finding of *N. asteroides* and failure to demonstrate the easily cultured *Sporotrichum* are believed to be firm evidence that this was nocardiosis and not sporotrichosis. As far as can be ascertained, nocardiosis presenting in this particular fashion has been previously reported only once.

The treatment of this condition deserves comment. The necessity for appropriate therapy of nocardiosis is stressed by Peabody and Seabury (1960) in their review of the treatment of this disease. Benbow *et alii* (in 1944) treated systemic nocardiosis with sulphonamides in two cases and obtained good results. Strauss *et alii* (1951) studied the effect of 14 chemotherapeutic substances both *in vitro* and *in vivo* in infected mice. Penicillin and neomycin were found to have little or no effect. A marked discrepancy was found between the in-vitro and in-vivo effects of the broad-spectrum antibiotics. *In vitro*, chlortetracycline, oxytetracycline and chloramphenicol were each capable of inhibiting completely most of the strains. *In vivo*, however, the best survival rate obtained was only 44%, with chlortetracycline.

Sulphadiazine, on the other hand, while not so effective *in vitro*, was capable of giving a 100% survival rate when given *in vivo* in the appropriate dosages. This observation was supported by Weed *et alii* (1955), who consider that the blood concentration of sulphonamides should be maintained at between 16 and 20 mg. per 100 ml. of blood. To ensure this, they suggest a daily intake of 6 to 10 grammes of sulphonamides. They state that in the presence of an adequate fluid intake this dosage can be maintained for several months.

Other authors have also noted a good response to sulphonamide therapy (Webster, 1956; Peabody and Seabury, 1957). The latter authors recommend a prolonged course of treatment, up to a year's duration, and favour combination of therapy with either streptomycin or one of the broad-spectrum antibiotics. Stilbamidine is stated to produce complete inhibition in concentrations attainable in man. Another agent which may prove of value in the treatment of resistant infections, and particularly of madura foot, is 4,4-diaminodiphenyl sulfone ("Dapsone"—Ochoa *et alii*, 1952; Rankin, 1960).

Ballenger (1957), in his review of 95 cases, found the mortality rate to be 68·4%; but half the patients who died had received no specific therapy.

In the present case, chlortetracycline and chloramphenicol were given prior to the patient's admission to hospital, but new nodules appeared despite this therapy. After his admission, erythromycin and triple sulphonamides were given, and, a little later, relatively high doses of iodides were employed. Arrest of the infection and clinical improvement seemed to follow on these measures.

Summary.

An example of infection of the hand and arm by *N. asteroides* and its successful treatment is described.

The mode of presentation, resembling sporotrichosis, was unusual, and, it is believed, this constitutes only the second such case reported in the literature.

Acknowledgements.

It is my pleasure to express my gratitude to Professor H. N. Robson for permission to publish this case report and for his help and encouragement in its preparation. I should also like to thank Dr. R. A. Russell for referring this patient to us, Dr. K. Anderson of the Institute of Medical and Veterinary Science for bacteriological studies and advice, and Dr. H. Lander, Dr. G. F. Donald and Dr. M. Tipping for their assistance.

References.

BAKER, R. D. (1957), "The Diagnosis of Fungus Diseases by Biopsy", *J. chron. Dis.*, 5: 552.

BALLENGER, C. N., and GOLDRING, D. (1957), "Nocardiosis in Childhood", *J. Pediat.*, 50: 145.

BENBOW, E. P., SMITH, D. T., and GRIMSON, K. S. (1944), "Sulphonamide Therapy in Actinomycosis", *Amer. Rev. Tuberc.*, 43: 395.

BUCHANAN, G., LURIE, H. I., and ROUX, P. (1948), "History of Actinomycosis in South Africa", *S. Afr. med. J.*, 22: 493.

CONANT, N. F., SMITH, D. T., BAKER, R. D., CALLAWAY, J. L., and MARTIN, D. S. (1954), "Manual of Clinical Mycology", 2nd Edition, Saunders, Philadelphia.

CULLEN, C. H., and SHARP, M. E. (1951), "Infection of Wounds with Actinomyces", *J. Bone Jt Surg.*, 33B: 221.

EPPINGER, H. (1890), *"Ueber eine neue pathogene Cladothrix und eine durch sie Hervorgerufene Pseudo-tuberculosis"*, *Beitr. path. Anat.*, 9: 287.

GOLDSWORTHY, N. E. (1937), "Pulmonary Actinomycosis Caused by an Acid-Fast Species of Actinomyces", *J. Path. Bact.*, 45: 17.

GUY, W. H. (1920), "Nocardiosis Cutis Resembling Sporotrichosis", *Arch. Dermat. Syph.*, 2: 137.

JOHNSTON, K. G. (1954), "Nocardiosis in Dogs", MED. J. AUST., 1: 534.

OCHOA, G. A., SCHIELS, J., and VASQUEZ, P. (1952), "Action of 4,4-diamino-diphenyl Sulphone on Nocardia Brasiliensis", *Gac. méd. Méx.*, 82: 345.

O'REILLY, M. J. J., and POWELL, R. E. (1953), "Report of a Case of Nocardial Infection in Australia", MED. J. AUST., 1: 703.

PEABODY, J. W., JUN., and SEABURY, J. H. (1957), "Actinomycosis and Nocardiosis", *J. chron. Dis.*, 5: 374.

PEABODY, J. W., JUN., and SEABURY, J. H. (1960), "Actinomycosis and Nocardiosis. A Review of Basic Differences in Therapy", *Amer. J. Med.*, 28: 99.

RANKIN, A. M. (1960), personal communication.

SMITH, D. E., and BENECKE, J. (1960), "Pulmonary Nocardiosis: Report of a Fatal Case", MED. J. AUST., 2: 254.

STRAUSS, R. E., KLIGMAN, A. M., and PILLSBURY, D. M. (1951), "The Chemotherapy of Actinomycosis and Nocardiosis", *Amer. Rev. Tuberc.*, 63: 441.

TUCKER, R., and MILLAR, R. (1953), "Outbreak of Nocardiosis in Marsupials in the Brisbane Botanical Gardens", *J. comp. Path.*, 63: 143.

WEBSTER, B. H. (1956), "Pulmonary Nocardiosis", *Amer. Rev. Tuberc.*, 73: 485.

WEED, L. A., ANDERSEN, H. A., GOOD, C. A., and BAGGENSTOSS, A. H. (1955), "Nocardiosis", *New Engl. J. Med.*, 253: 1137.

Reviews.

Clinical Disorders of the Pulmonary Circulation. Edited by Raymond Daley, M.A., M.D. Camb., F.R.C.P., John F. Goodwin, M.D. Lond., F.R.C.P., and Robert E. Steiner, M.D.N.U.I., M.R.C.P., D.M.R., F.F.R.; 1960. London: J. & A. Churchill Ltd. 9¼" × 7¼", pp. 376, with 133 illustrations. Price: 75s. net (English).

IT is impossible to resist probing further into a monograph on a complex subject where much is controversial and uncertain, when the opening sentence is: "Each lung is divided into ten bronchovascular segments." Indeed, even before this there is a minor surprise, for in the foreword (by Paul Wood), instead of the usual restrained eulogy, we find some pertinent observations on the terminology of pulmonary hypertension and cor pulmonale. Wood recognizes three types of the former—passive (venous), hyperkinetic and vaso-occlusive, the last-mentioned relating to increased pulmonary vascular resistance, whether obstructive, obliterative or functional in origin. Cor pulmonale he defines simply as "a disturbance of the cardiovascular system secondary to parenchymatous disease of the lungs or alteration in the thoracic cage". Professor John McMichael, in his chapter on chronic pulmonary heart disease, also includes cardiovascular disturbances secondary to primary disorders of the pulmonary vascular bed. Wood would deny these a place under the heading of cor pulmonale, and would classify them simply as producing pulmonary hypertension. It is not the place here to argue such points; but although there may be those who consider such niceties of classification mere hair-splitting, in our opinion definitive terminology is essential to clarity of thought and discussion. Throughout this work there is sufficient uniformity and sufficient care in definition to avoid confusion without in any instance begging the issues involved. No doubt this is largely attributable to the fact that six of the nine contributors come from the Postgraduate Medical School of London; their close association has also avoided the repetition frequently encountered in multi-author publications of this type.

The enthusiasm of the investigator frequently shines through the predominantly clinical approach—a "most unusual dog experiment", "preparations beautifully executed and carefully controlled". The research activities of the authors is also reflected in the up-to-the-minute references, many of which are dated 1960.

The anatomy and physiology of the pulmonary circulation are dealt with by Raymond Daley and Grant de J. Lee, and pulmonary function is admirably reviewed (except for Figure 13) by Kenneth W. Donald. Donald's criticism of the reluctance of British physicians and physiologists to use arterial puncture is not out of place in this country. Professor C. V. Harrison gives an excellent description of the relevant morbid anatomy, accounts of which are not readily available to the clinician in concise form. John Goodwin contributes the chapters on the nature of pulmonary hypertension, electrocardiography, mitral valve and left atrial disease and congenital heart disease, thus minimizing any overlap in these sections. The inadvertent substitution of "falls" for "rises" (page 278) in discussing the systemic pressure response to temporary occlusion of a patent ductus is too obvious to be seriously misleading. The chapter on radiology by Robert E. Steiner is valuable, but marred by inadequate and in part misleading diagrams of the arterial anatomy (Figures 22 and 23; surely better done, at increased cost, of course, by angiograms), and by many lists and tables which, combined with the free use of italic and bold type, are enough to give a compositor a hangover. Although the X-ray reproductions are generally reasonably good, they are often too small and as a result sometimes fail to make their point.

McMichael and Philip Hugh-Jones contrive to write on chronic pulmonary heart disease and chronic pulmonary disease respectively without undue overlap or conflict. The latter chapter attempts to cover an enormous amount of ground in 30 pages, and although competently written, it cannot help but be somewhat uneven. In a book which will be widely read by cardiologists, it is a pity that more space could not have been devoted to pulmonary disorders, for in cardiological textbooks they are poorly described, if at all. Both authors stress the "insensitive" respiratory centre, a half-truth which semantically closes the door on a concept which views the elimination of more carbon dioxide per litre of expired air as in some circumstances an ingenious homœostatic mechanism.

The standard of production is excellent, although the editors have overlooked many misprints (those on pages 41, 47, 203, 205, 322, 329, 345 do not form the full list), and the punctuation is inconsistent and frequently erroneous. The figures, diagrams and X-ray films might in some instances have been clearer if a little larger, a criticism applying particularly to those labelled in a curious fancy script which is often difficult to read, and in any case is out of place in a scientific work. The bibliographies are outstanding, and a special note of appreciation (in view of previous comments in these columns) is due for the inclusion of the titles of the papers listed.

Whether or not the criticisms voiced in this review are trivial is perhaps a matter of opinion; but there is no doubt at all that in spite of them this is an outstanding publication doing great service to British medicine. It gathers together much valuable information and indicates the trends of current research, gathering the best from Britain and integrating it well with work done elsewhere, a balance not always achieved in works of this kind. We strongly commend it to all with any interest in diseases of the heart and lungs.

Surgical Treatment of Unequal Extremities. By Charles Weer Goff, M.D.; 1960. Springfield, Illinois: Charles C. Thomas, and Oxford: Blackwell Scientific Publications Ltd. 11" × 8¾", pp. 194, with illustrations. Price: 88s. (English).

THIS is one of the series of monographs in "American Lectures in Orthopædic Surgery". The author is the Associate Clinical Professor of Orthopædic Surgery at Yale University School of Medicine. The book aims to present practical ways and means of managing the problem of inequality of leg length, with emphasis on the control of growth, and is a comparatively large volume of 184 quarto pages.

The subject matter includes methods of assessing bone length and growth, and methods of bone lengthening and shortening, with particular reference to growth stimulation and arrest. Then follow chapters on the pathological changes induced in the epiphyseal plate by stapling, the effect of fractures on bone growth, and some other problems of bone growth which are experimental studies. There is an extensive bibliography.

The book brings into one compass a considerable mass of information, part historical, and part the personal experience of the author at the Newington Hospital. The historical summaries will be of particular value to those interested in the lesser-known beginnings of this subject, and in methods now tried and rejected. The attempts to induce accelerated bone growth are well covered, and it is concluded that no reliable method is yet available. On the practical side, the author's experience leads him to prefer epiphyseal arrest by stapling, and he discusses in detail the several methods of bone-growth prediction which are available. He accepts epiphyseal arrest by grafting, and shortening of the femur or tibia when indicated. However, bone lengthening has

not been a happy experience, and he remarks that the last operation was done in 1938.

It would not be proper to avoid certain critical observations. The two-column system is employed, and the subheadings of the chapters are given very little emphasis, so that it is somewhat difficult to find any particular matter that is being sought. The illustrations are profuse, but many are unnecessary and simply interrupt the text. At times, too, one is perplexed by the admitted differences between American and British idiom. Finally, the book measures 8·5 in. by 11·25 in. This makes it an awkward shape for the shelves of a reference library, which is its proper place in our opinion.

The Rickettsial Diseases. By P. F. Zdrodovskii and H. M. Golinevich; translated from the Russian by B. Haigh, M.A., M.B., B.Chir.; 1960. Oxford, London, New York and Paris: Pergamon Press. 8½" × 5½", pp. 644, with illustrations. Price: £5 5s. (English).

THIS book is in two parts. The first deals with the pathogenic rickettsiæ, their classification, morphology, behaviour in arthropods and experimental animals, growth in eggs and tissue culture, variation in virulence, resistance to environmental factors, and serological reactions. A feature which will commend it to laboratory workers is that a great variety of techniques, those used in the U.S.S.R. and elsewhere, are described in detail. (However, the composition of the cell-free medium on which some claim to have grown *Rickettsia quintana* is not disclosed.) Precautions that should be taken to avoid laboratory infections are noted.

The second part of the book deals with the clinical features, pathology, chemotherapy, epidemiology, prevention and comparative immunology of the individual rickettsioses, of which at least eight are prevalent in the U.S.S.R. Considerable Russian work on these is here brought conveniently to the English reader. They include epidemic typhus; murine typhus, which is present in the Black Sea and Caspian regions; *fièvre boutonneuse*, in the same areas; "Q" fever, common and widely distributed; a type of tick typhus in North Asia caused by *R. sibiricus*; rickettsialpox; trench fever; and "paroxysmal rickettsiosis", spread by the tick *Ixodes ricinus*. The accounts are by no means confined to Russian work; foreign observations are adequately reviewed, and descriptions are included of such diseases as scrub typhus, Rocky Mountain fever and North Queensland tick typhus, not present in the U.S.S.R. There are over 300 references to the Russian and over 600 to the foreign literature. These date up to 1957.

On the whole, the translation reads satisfactorily. There is an occasional curiosity, such as "rickettsial virus" or "hard enough vacuum". The word "tick" is frequently used instead of "mite", and "group" instead of "genus". Many authors' names are misspelt. A reference on page 375 to "Q" fever in New Zealand is incorrect; the cases described by Adams and other New Zealand medical officers arose among troops in Italy.

This is the first attempt of which we are aware to provide in one volume a comprehensive account of all the rickettsioses. It is a creditable achievement, and will be welcomed by all those who are interested in this group of diseases, whether in the wards, the laboratory or the health office.

The Principles of Surgical Nursing. Edited by Thomas F. Rose, M.S., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S.; 1960. Sydney: Dymock's Book Arcade Ltd. 8¼" × 5½", pp. 642, with many illustrations. Price: 45s.

ANYONE who accepts the responsibility of editing a book which sets itself out to deal with the "principles" of a subject immediately lays himself open to the criticisms of every reviewer who feels that he knows best what restriction in content, and what variation in emphasis, the use of such a title requires. We certainly think that Mr. Rose is more than vulnerable on this score. That he and his collaborators have produced a textbook which is comprehensive enough to be acceptable to even a good medical undergraduate there can be no question; but most of the fundamental nursing principles are conspicuous by their absence. Surely the essential things with which a nurse is deeply concerned relate to happenings such as the healing of wounds and the event of infection. The most urgent problem of our surgical wards is the scourge of wound infection, and our deepest concern the dissemination of the resistant staphylococcus. A nurse should have an understanding of the value and shortcomings of antibiotic therapy, and more than an inkling of what we hope to achieve by gastric suction and by intravenous therapy. Topics such as these do not, to our way of thinking, feature nearly as prominently as they deserve. Even the commonplace of a Colles' fracture is dismissed in eight lines, whereas coarctation of the aorta is allowed 24.

We will, however, hasten to add that the sections dealing with the specialties are in the main well written. Our quarrel is only with the unreasonableness of the emphasis which is given to their consideration.

It is commendable in producing a book for nurses to try hard to keep the price as low as possible (and this is a cheap volume at 45s. in Australia); but it would surely have been worth while to invite a heavier investment, and to offer something better than the very indifferent paper and print of the present publication. There are many spelling mistakes. "Wangansteen" appears very many times, and "Perthes" has been misspelled often enough over the years to make "Perthe" quite inexcusable.

If Mr. Rose will consent to change the title of his book to "A Textbook of Surgical Nursing", we may be prevailed on to induce our ward sister to buy a copy for reference; but if he persists in calling it "The Principles of Surgical Nursing", we will advise her rather to buy a new hat.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Thrombosis and Anticoagulant Therapy", proceedings of a Symposium arranged by Professor P. A. Owren, Professor R. B. Hunter, and Dr. W. Walker, held in Queen's College, Dnndee, on 29th and 30th September, and 1st October, 1960, edited by W. Walker; 1960. Edinburgh, London: E. & S. Livingstone Ltd. 9¾" × 7½", pp. 106, with illustrations. Price: 17s. 6d. net (English).

"System of Ophthalmology: Volume II, The Anatomy of the Visual System", edited by Sir Stewart Duke-Elder, G.C.V.O., F.R.S., M.A., LL.D., D.Sc., M.D., D.M., F.R.C.S., F.R.C.S.E., F.A.C.S., F.R.A.C.S.; 1961. London: Henry Kimpton. 10" × 7", pp. 902, with illustrations. Price: 130s. (English)

"Surgery of the Esophagus", by R. W. Postlethwait, M.D., and W. C. Sealy, M.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 11" × 8½", pp. 482, with illustrations. Price: £12 (English).

"Surgical Diseases of the Lung", by B. H. Burch, M.A., M.D., and A. C. Miller, M.S., M.D., F.A.C.S.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 10" × 6¾", pp. 128, with illustrations. Price: 68s. (English).

"Keeping Fit for All Ages: Know the Game Series"; 1961. London: Educational Productions Ltd. 5½" × 8", pp. 40, with illustrations. Price: 2s. 6d. (English).

"The Annual of Czechoslovak Medical Literature, 1958", by Státní Lékarská Knihovna (National Medical Library); 1960. Praha: Státní Zdravotnické Nakladatelstvf. 8¼" × 5¾", pp. 624. Price not stated.

"Public Health Aspects of Low Birth Weight: Third Report of the Expert Committee on Maternal and Child Health", World Health Organization Technical Report Series, No. 217; 1961. Geneva: World Health Organization. 9½" × 6½", pp. 16. Price: 1s. 9d.

"An Approach to Old Age and its Problems", by Margaret Neville Hill, C.B.E.; 1961. Edinburgh, London: Oliver & Boyd. 8½" × 5½", pp. 132, with a few illustrations. Price: 25s.

"Cholera: Its Pathology and Pathogenesis", by S. N. De, M.B., D.T.M. (Calcutta), Ph.D. (London); 1961. Edinburgh, London: Oliver & Boyd. 8¼" × 5½", pp. 142, with illustrations. Price: 43s. 6d.

"Handbook of Surgery", edited by J. L. Wilson, M.D., and J. J. McDonald, M.D.; 1960. Los Altos, California: Lange Medical Publications; Melbourne: Ramsay's Medical Books. 7" × 4", pp. 646, with illustrations. Price: 42s. 9d.

"Handbook of Pediatrics", by H. K. Silver, M.D., C. H. Kempe, M.D., and H. B. Bruyn, M.D.; fourth edition; 1961. Los Altos, California: Lange Medical Publications; Melbourne: Ramsay's Medical Books. 7" × 4", pp. 577. Price: 37s. 3d.

"The Nuffield Provincial Hospitals Trust, Fifth Report: A Record of the Progress of Schemes and Descriptions of New Projects 1958-1961"; 1961. London: The Nuffield Provincial Hospitals Trust. 8¼" × 5½", pp. 124. Price not stated.

The Medical Journal of Australia

SATURDAY, AUGUST 19, 1961.

STIRRING OF THE ACADEMIC WATERS.

Now, as far as our Australian universities are concerned, it is of great satisfaction to us all, I think, that there has been such a stirring of the waters, first of all with the formation of the Murray Commission and, later, of the Universities Commission which has just issued a very excellent report, and the rise of the new universities in Australia of which the University of New South Wales is one.

So commented Sir Richard Boyer (since to our great loss deceased) in his introduction to a symposium[1] on "The Australian Universities—1970" held at the University of New South Wales in December, 1960. Sir Richard went on to point to the steadily growing demand for tertiary education in a great many walks of life and the need for a general appreciation of university requirements. Referring to what was spoken of as "the human predicament", Sir Richard said that it seemed to him that the modern world was caught up in a situation in which the remedy for this human predicament was not less but ever more and more education at a high level, the spreading not only of secondary education which had been seen in the present time, but tertiary education further and further afield amongst the community. Complementary to this is the point raised by the Chancellor of the University of New South Wales, the Honourable J. S. J. Clancy—that the common opinion, perhaps the general opinion, in Australia, is that everyone has the right to a university education. Thus with the growing demand for graduates in the life of the community and the increasing desire of those qualified to undertake university courses combined with a steadily rising national population and, more important, a disproportionately rising youth population, the problem becomes ultimately one of providing sufficient and satisfactory university facilities.

In a general survey of the situation the first main speaker in the symposium, Mr. W. H. Maze, Assistant Principal of the University of Sydney, presented figures to show the expected great increase in student numbers during the next decade and suggested that this called for consideration of at least three alternatives: (*a*) the existing university should admit more students; (*b*) new university foundations should be established; (*c*) a number of institutions should be founded outside the university which would cater for some of the needs of professional and technical training. On the question of increase in the size of existing universities, Mr. Maze said that in Australia the tendency had been to ask the universities to accept further burdens or even to absorb sub-graduate functions which rightly belonged to a technical college. He considered that if universities were to fulfil the central functions of education of students up to the highest possible level and to carry on scholarship and research, then they must not only resist some of the types of demands which had been made on them in the past, but also refuse to be responsible for such activities. However, he was clearly not on the side of those who would keep universities small. Provided that certain criteria were satisfied at each stage of growth, he could see advantages in bigger and bigger universities, particularly in relation to the increased number of senior staff, who helped to provide a more balanced atmosphere in any one department, and the practicability of providing the more elaborate and expensive equipment generally required, not only in the technological departments, but by many teachers of the humanities. He put forward three criteria on which the principal growth rate was determinable: (i) the standards of teaching and examination for degrees, (ii) the rate of attracting and retaining staff of genuine university calibre, (iii) the vitality and rate of expansion of the university's research programme. On this basis, he suggested, a university could continue to grow as long as it continued to function as a university. "It should not be allowed to grow if pressure from the community for more and more graduates leads to the lowering of standards of teaching and examining, to the appointment of only reliable routine teachers, and to the neglect of research." As is generally realized, these criteria are stiff, especially as they involve finding staff of the right quality. The staff dilemma is not lessened and may even be increased by looking to the alternative of finding new universities. Mr. Maze examined in some detail the question of where staff might be expected to come from and where they had come from in the past. He concluded that the onus was on universities to set about the task of attracting, training and retaining young academics if requirements were to be met. Special financial provision for the encouragement of young research students and for the employment of all available junior staff would be a wise insurance for the future. To cope with world-wide competition for staff, standards and facilities in Australian universities had to stand comparison with those overseas. In stressing the importance of removing from universities tasks which were not properly theirs, Mr. Maze urged the foundation and expansion of other tertiary institutions, such as teachers' colleges, technical colleges, institutes of technology, agricultural colleges and dramatic, music and library schools. In conclusion he referred to the provision of adequate advances for university development and, despite recent favourable developments, displayed little optimism that enough money would be forthcoming from the public purse to meet the needs. We hope, for the sake of the community as a whole, that his predictions will prove

[1] "The Australian Universities—1970". Papers presented at the Symposium on "The Australian Universities—1970", held at the University of New South Wales on December 6, 7, 1960. Published by The University of New South Wales, Sydney. 9½" × 7", pp. 80. Price: 17s. 6d.

unduly gloomy. Commenting on Mr. Maze's presentation, Mr. J. O. A. Bourke, Bursar of the University of New South Wales, stressed our need to reconcile ourselves to big universities because the provision of new universities is at best a long-term project and cannot be expected to meet immediate pressing requirements.

The Vice-Chancellor of Monash University, Dr. J. A. L. Matheson, made a contribution to the symposium important out of all proportion to its brevity. His thoughts centred around the point that universities had always had a dual rôle — teaching and creative intellectual activity; the latter meant research, in the sense of elucidation of facts in the sciences mainly, and criticism, in the sense of elucidation of ideas in the arts mainly. Justification for this rested on two beliefs—that it was in the public interest that inquiries should be pursued in an environment free of the restraints necessary in almost all other institutions where research was undertaken, and that teaching at this level could not be adequately undertaken unless a high proportion of the teachers was engaged in individual creative work. This was the reason why, if it became necessary to narrow the spectrum of ability to enter the university, the choice must always be in the direction of reserving the universities for the most able students. Other tertiary educational establishments had their place, but it was confusing to call them universities. At the same time Dr. Matheson pointed out that, even if they had only the most able students, the universities could still not predict their future careers and tailor their courses accordingly; it was therefore most important to develop the students' capacity for self-education throughout life. Turning to the vexed problem of difficulties and failures in the first year of most university courses, Dr. Matheson suggested several possible lines of solution, but did not seem much impressed with any of them. On the question of how universities could be educative in the broader sense, he saw little hope of fitting all that was required into the undergraduate's curriculum and looked to a possible solution in the expansion of post-graduate courses. Of a further series of problems briefly raised by Dr. Matheson we may refer in particular to that of the adequate use of university buildings, which cost a great deal of money but are not used fully because of the limited working day and the length of vacations. Perhaps they may be used more, but experience in some other universities suggests the need for caution. Allied to this problem is that of university residence. This is most valuable in student education, but faces similar problems of cost and limited use of facilities. It is important to find even a partial solution.

The third main speaker, Professor D. W. Phillips, Pro-Vice-Chancellor of the University of New South Wales, was forthright and bold in his presentation. Looking at the question of the needs of the next ten years, he showed little patience with "the idea of solving our problems by merely closing our doors". He produced figures of estimated costs if university facilities were to be expanded to the point necessary to take all comers at present entrance standards, but suggested that the sum needed was not a large investment to ensure the proper education of the great number of graduates needed for Australia's future. Professor Phillips saw some hope in the large institution, operating perhaps on several different sites, in which the influence of a restricted number of experienced senior professors and lecturers could be spread over a larger number of junior but less experienced teachers. Discussing the pros and cons of small and large universities, Professor Phillips suggested that the advantages of a small university disappeared at a point well below the present size of most Australian universities, and that further increases in size did not necessarily aggravate the position. Indeed, there were greater possibilities of solution of our difficulties in the really large institutions as against those of middle size. Professor Phillips' full and informed discussion of the question of size of universities cannot be summarized here, but it should be examined by all concerned with this problem. It is interesting to note that he envisioned the expansion of the University of New South Wales as a multi-campus institution of considerable size and concluded: "Size—bigness—is not a thing to be frightened of provided it is well organized and controlled."

The last subject discussed was "The University and Industry", an aspect of the subject not always considered by the sort of academic mind that loves the ivory tower, but one of increasing pertinence in our community. The speaker, Mr. J. C. Richards, General Manager, Development and Shipbuilding, of the Broken Hill Proprietary Co. Ltd., commented by way of introduction: "The continuation of Australia's size, isolation, small population and the current industrial growth present unique problems in tailoring tertiary education to meet the demands of industry." This he proceeded to elaborate with an impressive mass of facts and considered arguments. If he tended to convey the impression that the university's only rôle, or at most its main rôle, was to feed industry with appropriately prepared graduates, the apparent bias was probably justified to make sure that the point was made. Perhaps the balance has been too long in the opposite direction.

It would be hopeless to attempt any adequate summing-up of the material presented by the four main speakers in this symposium and by the many who contributed to the discussion. All concerned with the subject — and that should include most graduates, including medical graduates—need to study the symposium for themselves. It is good indeed to see the great stirring of the waters in university matters — the growing demand of the community for graduates in all sorts of fields, the willingness for those in high places to provide finance far beyond the dreams of a few years ago, the awakening of new hope and vision and even originality of ideas in academic circles. Perhaps the one point that needs to be made is that, in considering the future of university education, we must cast aside prejudices and aim to determine what Australia and the Australian people need to meet the demands and opportunities of today and of the future. The needs of today and tomorrow differ in many ways from those of yesterday and are pressing. If these needs seem to be beyond our financial resources, we must in this context ponder clearly and honestly the paradoxical question: can we afford to do without what we cannot afford?

Comments and Abstracts.

POLIOMYELITIS IN AN IMMUNIZED COMMUNITY.

THE abrupt drop in the incidence of poliomyelitis after the institution of immunization with Salk-type vaccines has been a world-wide experience wherever effective campaigns have been launched. Nevertheless, the experts have continued to warn us that some of this may have been due to the natural epidemic cycle of the disease, and that we should not allow ourselves to be lulled into complacency. From 1959 onwards, evidence has been accumulating that poliomyelitis epidemics can still occur, even in relatively well-vaccinated communities. R. T. Ravenbolt[1] has recently published a very interesting account of just such an epidemic, which occurred in Seattle-King County, Washington, during 1959. Unlike Britain, where poliomyelitis did not appear as an epidemic disease till 1946, Seattle recorded its first poliomyelitis epidemic in 1910, and thereafter the disease occurred with a natural periodicity of about three to four years between epidemic peaks till 1948. Between 1948 and 1955 reported morbidity was sustained at the high level of about 20 cases per 100,000 population *per annum*. Beginning in 1955, and coinciding with the introduction of the Salk vaccine, there was a steep decline in the incidence of the disease to less than one per 100,000 in 1957 and 1958. Then in the second half of 1959 a sharp epidemic occurred due to a Type I poliovirus which produced morbidity and mortality rates approaching those observed during the bad years of 1950-1954. There were altogether 113 cases of paralytic poliomyelitis with eight deaths in a population of a little less than one million.

The vaccination status of the population at the beginning of the epidemic was known fairly accurately from a survey conducted by telephone for some other purpose (some 80% of households possessed a telephone); 77% of persons under 40 years old had received three or four injections of vaccine, 10% had received one or two injections, and 13% were unvaccinated. The epidemic provided a number of instructive features. An unusually large proportion of the patients (three-fifths) were adults. The epidemic reached its peak among the children two weeks before the first peak in the adult population, and nearly all adult patients had had regular household contact with children during the month before the onset of their illness; the majority came from households with pre-school children. This confirms the findings of other investigators that poliomyelitis tends to spread among children, especially those of pre-school age, and that adults acquire the infection chiefly from children with whom they are in close contact. This pattern is easily explained if we assume that dissemination is chiefly by fæcal contamination. Another interesting feature of the epidemic was that, unlike epidemics before vaccination became available, in which the incidence tended to be more severe in the better residential areas, on this occasion the great majority of cases occurred among residents of low-income housing areas. This is explained by the fact that, in spite of the provision of free immunization facilities and repeated campaigns during the previous three years, the immunization status of these communities was below average. It also probably reflects the elimination of the virus as an endemic infection in the low-income communities; these had presumably been previously partly protected by natural immunity acquired from a high level of endemic infections in infancy.

As might be expected, the incidence of paralytic disease was highest among the unvaccinated. Two-thirds of all cases occurred among those who had received no immunizing injections, and a further 10% among those who had received only one. However, 19 cases occurred among those who had received three injections, and one three-year-old boy who had received four optimally spaced injections developed paralytic poliomyelitis five weeks after his last injection. Further, there was no evidence that the disease was any less severe in patients who had received an apparently adequate course of immunizing injections than in the unvaccinated. One satisfactory feature of the epidemic was the fact that only two cases occurred in pregnant women, a reward for the special efforts made to extend immunization in all cases of pregnancy. This is also the probable reason for the reversal of the usual sex ratio among adult patients; in the 1954 epidemic only 33% of adult patients were male, whereas in the 1959 epidemic men made up 66% of the adult patients.

It was known that the immunization status of members of the Christian Science church was poor, so inquiry was made as to the religion of victims of the epidemic. Only three of the 113 unvaccinated patients signified membership of this church, and Ravenbolt concludes that religion was not the principal reason for non-vaccination. He blames "procrastination, apathy, ignorance, fear of needles, and doubts concerning safety of the vaccine". An inquiry into the tonsillectomy status of patients showed that only one had undergone tonsillectomy within six months of contracting poliomyelitis. (This patient developed poliomyelitis 19 days after tonsillectomy, experienced a mild attack of the bulbar type, and made a complete recovery within four weeks.) Among those who had had tonsillectomy performed more than six months before contracting the disease, the incidence of bulbar paralysis was no higher than among those who had no history of tonsillectomy. Fear of contracting poliomyelitis, as well as coolness of the weather, led to a virtual cessation of public bathing after mid-August, but this had no apparent effect on the course of the epidemic and there was no evidence from patients' histories that swimming was a significant factor in the epidemiogenesis of the outbreak.

In his discussion of the epidemic Ravenbolt examines the widely held view that Salk vaccination does not affect the propagation and distribution of poliovirus, and concludes that there are good reasons for doubting the validity of this belief. He shows that some of the studies usually quoted in support of this view are by no means conclusive, and that some of the data could be held to support the opposite conclusion, namely that immunization with Salk vaccine "causes moderate reduction in the frequency, duration and titer of alimentary poliovirus infection". He considers that this interpretation of the data is supported by the changed epidemiological pattern of poliomyelitis occurrence observed since vaccination was begun. He holds that the abrupt change in the relative incidence of poliomyelitis in the lower socio-economic groups observed in the Seattle-King County outbreak, and elsewhere, indicates a fundamental disturbance of poliovirus ecology, probably due to vaccination. He suggests that, if this is so, eradication of poliovirus from large populations by more nearly universal immunization with Salk vaccine may be possible, and as a corollary of this, he stresses the importance of achieving early vaccination of pre-school children in the lowest socio-economic group, as these children are at present the prime propagators of poliovirus (as well as of many other infective agents). He summarizes his conclusion in these words:

> This outbreak was probably due especially to accumulation of an unusually susceptible preschool population in public housing projects and similar low socioeconomic groups. This accumulation indicates unusual lack of natural immunization which, with the very low incidence of poliomyelitis during recent years and the changes in racial, socioeconomic, and geographic distribution of cases, suggests that extensive use of Salk vaccine did temporarily limit propagation of poliovirus in this community.

In a very recent paper G. W. A. Dick *et alii*[2] suggest that the apparent community-protective effect of Salk vaccine may be due to a reduction in pharyngeal transmission of virulent poliovirus. They base this suggestion on their finding that Salk vaccination can prevent virus multiplication in the throat, though not in the bowel.

[1] *Pub. Hlth Rep. (Wash.)*, 1961, 76: 166 (February).

[2] *Brit. med. J.*, 1961, 2: 266 (July 29).

We may compare these findings with those of a rather less well documented outbreak which occurred at the same time in Tennessee, and is the subject of a paper by R. E. Merrill, R. Batcon and D. Kinsman.[3] This outbreak was also due to a Type I virus. Sixty-nine patients were accepted as cases of poliomyelitis, all but two having paralytic symptoms. The age distribution of these cases was very different from that in the Seattle outbreak, half the cases being in pre-school children and a further quarter among those aged five to 10 years. The authors of this account do not indicate the vaccination status of the community involved, but 43 out of 67 cases occurred among those who were unvaccinated, and only three occurred among those whom they regard as "fully protected"—that is, who had received a third or fourth injection within the previous 12 months; four other cases occurred in persons who had received three injections, the last more than 12 months previously. Merrill and his colleagues had set out to evaluate the relationship of vaccination status to the degree of paralysis in affected patients. As already noted, the number of cases in their best immunized groups was very small, but like Ravenbolt they could find no evidence that, in patients who acquired the disease, there was any connexion between immunization status and severity of the disease.

Finally, we should perhaps emphasize the fact that, while the vaccines employed in these communities clearly did not give 100% protection, and while those who contracted the disease apparently fared equally whether they had received a full immunizing course or were totally unvaccinated, both epidemics provide ample evidence that the vaccines did provide full protection in a high proportion of cases. Why immunizing injections failed to confer immunity in a small proportion of cases is not understood, but that is the common experience of all immunizing procedures; it remains to be seen whether a vaccine of the Sabin type can achieve any better results.

NEURAL INTEGRATION IN SYSTEMIC PATHOLOGY.

STEWART WOLF[1] has lately commented on the general manifestations of many diseases usually regarded as local. Diseases which seem to involve a single organ may have widespread effects which are usually nicely patterned. This response Wolf regards as an adaptive function of the nervous system. Neural integration is complex and involves receptor and effector activity, and something connecting the two. This roundabout path may include the cerebral cortex. Reception, according to Wolf, is not sensation, and effector activity is not only motor or vasomotor; the ultimate effector pattern often depends on the peculiar significance of a circumstance and the past history of the patient.

Recent neurophysiological research has shown that everything in the body influences and is influenced by the brain. Wolf recalls the doctrine of "neurism" of Botkin (of Russia) a century ago, and the enormous body of evidence accumulated by Pavlov's successor Bykov. When symptoms come from the central nervous system they are not psychogenic in the sense of being due to a psychological conflict. The anatomical and physiological pathways are there, and the symptoms depend on the higher integration of complicated patterns. Wolf considers that placebos do a great deal more than placate and pacify. Placebo effects derive from the significance to the patient of the whole situation surrounding the therapeutic effort. It implies a connexion between a particular end organ and the interpretative areas of the brain. Distinctions between physical and mental disease, Wolf states, have little meaning, since the brain is an integral part of the whole human organism. It is futile to search for single causes for diseases; there is evidence for the modulating power of the nervous system on all sorts of noxious experiences. A disease arises more commonly from the effort of the body to deal with adverse forces than from the direct effect of the adverse stimulus on the organism. Each person reacts differently from all others, and the reaction depends on heredity, previous disease and other conditioning effects.

In biology the only permanent thing is change, requiring new adaptive responses on the part of organisms, races and species. We must look for the forces which arouse and the mechanisms which modulate the adaptive efforts of the nervous system. All this, Wolf writes, calls to mind the dictum of Osler: "It is much more important to know what sort of a patient has a disease than what sort of disease a patient has."

[3] *Amer. J. Dis. Child.*, 1960, 100: 857 (December).

[1] *Perspect. Biol. Med.*, 1961, 4: 288 (Spring).

SHORTER ABSTRACTS.

HYGIENE.

CHRISTMAS DISEASE AND COAL-MINING: TRAUMA AND EXPOSURE TO NITROGLYCERINE AS OCCUPATIONAL HAZARDS. C. B. KERR, *Brit. J. industr. Med.*, 1961, 18: 47-52 (January).

THE author describes a family of coal-miners who suffer from Christmas disease. The affected male members of two generations have spent their working lives underground. Three of the eight affected miners were temporarily severely disabled by episodes associated with their bleeding diathesis, and one died in 1894 from hæmorrhage as the result of an injury. A mild degree of Christmas disease caused an increased occupational morbidity in some members of the family, but did not shorten their over-all working life. Twelve other cases of Christmas disease in persons of employable age are briefly discussed. One patient had a cerebral hæmorrhage, possibly associated with the physiological effects of contact with nitroglycerine. A review of the literature suggests that nitroglycerine may have a significant ætiological action in the development of cerebral hæmorrhage in men with a defective hæmostatic mechanism. The author suggests that an analogous situation may exist in patients under anticoagulant treatment, who use nitrates or other vasodilator drugs therapeutically.

COPROPORPHYRINURIA IN GROUPS OF WORKERS AS AN INDEX OF INORGANIC LEAD ABSORPTION. R. H. ZIELHUIS, *Brit. J. industr. Med.*, 1961, 18: 58-62 (January).

THE author has investigated coproporphyrinuria in workers exposed to lead in order to establish levels in urine which would indicate lead absorption, and which could be used as criteria in the prevention of lead intoxication. An apparatus constructed by Donath enabled semi-quantitative determinations to be made sufficiently easily, quickly and accurately for screening purposes. In this method the intensity of fluorescence produced when ether-glacial acetic acid is shaken with the urine being tested is compared with the intensity of standard fluorescence on a scale numbered from 1 to 8. Each degree of the scale corresponds to a known concentration of coproporphyrin. The normal level found by examining the urine of 112 males not exposed to lead was 1·4 degrees. A total of 513 workers exposed to varying lead-in-air concentrations were then examined. Similar frequency distributions of coproporphyrinuria were found to be present in groups exposed to the same lead-in-air concentrations. Therefore by means of frequency distributions of coproporphyrinuria in a group of workmen it is possible to estimate the lead-in-air concentration in the air to which the group is exposed. Frequency distributions of hæmoglobin values for the same groups were then done and the correlation between the percentage of exposed persons with lowered hæmoglobin values and the percentage with raised coproporphyrinuria was found to be high. The frequency distribution of coproporphyrin values in a group therefore gives some indication of the degree of anæmia in the same group. The author concludes that an average coproporphyrin value above 1·5 degrees on the Donath scale in a group indicates increased lead intake. If between 1·5 and 2·5 degrees the exposure is within allowable limits. If above 2·5 degrees the concentration of lead in the air is probably above the maximum allowable concentration.

The degree of air pollution with lead and the degree of anæmia due to lead intake can be roughly estimated from the frequency distribution of coproporphyrinuria in a group. Individual counting of punctate basophils and estimation of hæmoglobin values becomes necessary when coproporphyrinuria values exceed the allowable range.

EROSION OF THE TEETH DUE TO SULPHURIC ACID IN THE BATTERY INDUSTRY. D. Malcolm and E. Paul, *Brit. J. industr. Med.*, 1961, 18: 63-69 (January).

THE authors report an investigation into the effects of sulphuric acid mist on the teeth of workers in the battery manufacturing industry. They examined 165 men exposed to acid fumes in forming and charging sections of the industry and compared them with 117 men in two other sections where the environment was free from acid. In both groups, effect on teeth of exposure, degree to which each tooth was affected, condition of mouth, number of decayed, missing and filled teeth, relation of resting lip level to level of erosion, breathing habit and medical history were noted for each man. Tooth lesions were classified into four groups; these were those showing: (*a*) loss of tooth substance due to trauma or excessive wear; (*b*) etching of labial enamel; (*c*) minor loss of tooth substance; (*d*) loss of more than half of tooth crown. A significant difference in the incidence of erosion was found between those exposed and those not exposed to acid fumes. The degree of erosion varied directly with the concentration of acid in the air, the length of exposure and the area of teeth not protected by the lips. The authors conclude that loss of tooth substance is due to gradual erosion by direct impingement of acid mist on exposed tooth surfaces. Methods of prevention are discussed briefly. The authors consider that transparent face shields and protective films deposited on the teeth that remain effective against acid for at least four hours are the two most effective means of protection.

METHYL BROMIDE POISONING. E. M. Rathus and P. J. Landy, *Brit. J. industr. Med.*, 1961, 18: 53-57 (January).

THE authors report seven cases of methyl bromide poisoning among workers using methyl bromide as a fumigant. Safety precautions taken included the wearing of respirators fitted with gas canisters effective against methyl bromide, and education of workers in regard to the risks involved. In spite of precautions severe cases of poisoning occurred. It was noticed that three of the poisoned persons had severe erythema on parts of the face covered by the respirator, indicating the presence of free methyl bromide in the inspired air. On testing it was found that canisters in the respirators of the affected workers gave no protection at all against methyl bromide. Other unused canisters from the same batch as the defective ones were also found to be faulty. Following this episode blood-bromide surveys were carried out at frequent intervals. These enabled an estimate to be made of the efficiency of safety precautions. Conways' microdiffusion method of estimating the level of bromide in blood was used. The author considers that this is the most reliable method and if bromide is present in any worker's blood, a reinspection of equipment and precautions is indicated.

AIR POLLUTION CONTROL IN URBAN PLANNING. L. Schreibeis *et alii*, *Amer. J. publ. Hlth*, February, 1961.

THE authors discuss means taken to reduce air pollution in the city of Pittsburgh. For nearly 150 years Pittsburgh has hoped to reduce smoke, and since 1892 laws to control smoke have existed. By 1940 the smoke nuisance had become so great that it threatened the economic future of the city. A Smoke Control Advisory Committee was appointed, and a unified smoke control programme administered and enforced by the Local Health Authority was adopted. Two broad categories of smoke pollution sources were delineated. These were: (i) industry, which includes manufacturing transportation, and service industries, and (ii) public activities, which include backyard burning, domestic fires and automobile operation. Air contaminants considered by the authors to be of the greatest significance are particulate matter of all sizes, sulphur dioxide and trioxide, hydrogen sulphide, oxidants, oxides of nitrogen and organic vapours. A great reduction in smoke pollution in recent years is due to a shift from the use of coal to gas in the home, and to a change in the transportation industries from engines using coal as a source of power to diesel oil engines. In addition to smoke reduction, the insoluble dust fall-out in some parts has been reduced from 97 tons per square mile per month to 39 tons. Prevention of air pollution is expensive and in order to have equitable and effective community-wide control the authors consider that laws and ordinances that are enforced are necessary. Legislation to control air pollution usually sets up emission limits for smoke and various other solids described as dust, fume, fly ash, cinders or particulate matter. There is a trend in recently introduced legislation to specify emission limits for various types of processes and to prohibit specific industries or restrict them to defined areas. The authors conclude by stating that the direct rewards of smoke elimination are great, but the indirect rewards can be incalculable in value and among the latter can be restoration of civic pride, courage and determination—the fundamental qualities on which all community progress rests.

AN EPIDEMIOLOGICAL APPROACH TO THE PROBLEM OF RISING NEONATAL MORTALITY IN BALTIMORE. K. Buetow, *Amer. J. publ. Hlth*, February, 1961.

A RISE in the neonatal death date occurred in Baltimore, U.S.A., in 1957 and 1958, and the author has investigated the factors present at the onset of and during pregnancy, labour and delivery, and factors affecting the child after delivery, at two large teaching hospitals where rises in neonatal mortality had been reported. The results were then compared with those obtained from an investigation of similar factors in 1956, the most recent year of significantly lower neonatal mortality. The author concludes from statistical data that at one hospital there were possible direct relationships between the rise in neonatal mortality and the following factors: (i) a rise in the proportion of patients failing to seek prenatal care, (ii) an increase in the incidence of puerperal morbidity, (iii) a change in the age distribution of the neonatal deaths, with an increase in the proportion of infants becoming ill and subsequently dying after the first 48 hours of life, (iv) an excess dosage of chloramphenicol in the newborn, particularly premature infants. In contrast, these factors played no significant rôle in the increase in neonatal mortality at the other hospital, where a rise in the number of premature deliveries alone was sufficient to account for their slightly elevated neonatal mortality rate.

RELATIVE EFFECTIVENESS OF DIETHYL TOLUAMIDE AND M-2020 AGAINST AEDES SCAPULARIS. F. W. Whittemore *et alii*, *publ. Hlth Rep.* (*Wash.*), 1961, 76: 179-182 (February).

FIELD TESTS of the relative effectiveness against the mosquito *Aedes scapularis* of the standard United States Army insect repellant M-2020 and di-ethyl toluamide at various dilutions and under various test conditions were carried out. Compared with the current standard Army formulation, diethyl toluamide appears to be markedly superior when tested at equal concentrations. On the other hand diethyl toluamide at 75% strength gives protection approximately equal to that obtained with the current Army standard at 100% strength, although it is markedly superior to the standard from the standpoint of resistance to removal by rubbing. Details of testing methods used are given together with tabulated results of tests.

FLUORESCENT ANTIBODY METHOD OF DETECTING GONORRHEA IN ASYMPTOMATIC FEMALES. A. Harris *et alii*, *Publ. Hlth. Rep.* (*Wash.*), 1961, 76: 93-96 (February).

THE authors discuss the value of the fluorescent antibody method of detecting gonococci in asymptomatic females. Two hundred and thirteen female prisoners with no signs or symptoms of gonococcal infection were examined, and gonococci were found in swabs taken from the cervical, urethral and vaginal areas of 44 of those examined. Examination of swabs from all three areas of the same patient resulted in more patients being found with positive results than would have been found if swabs from only one or two areas had been examined. Repeat examination showed the presence of gonococci in patients with a previous negative result. The authors consider that this investigation indicates that large numbers of females may be infected with gonococci without having signs or symptoms of gonococcal infection, and be a source of gonococcal infection in the community, and that the fluorescent antibody method is a rapid and effective means of finding them.

On the Periphery.

THE PRESERVATION OF HISTORY.

THE following statement has been made available by the Commonwealth Scientific and Industrial Research Organization.

Scientists from C.S.I.R.O. and the Defence Standards Laboratories of the Department of Supply have been hard at work in recent months devising a container for a rare historical relic. The relic is a specimen of the Magna Carta, one of the 14 that exist of any of the issues of Magna Carta. The Australian copy, which was purchased in 1952 by the National Library, is one of the only three surviving originals of the "Inspeximus" issue, which represents King Edward I's confirmation of the Great Charter in 1297, in the form in which it is found printed in the Statutes of the Realm today.

King John's Charter, granted at Runnymede in June, 1215, was annulled in August of the same year, having had legal force for only nine weeks. New versions, greatly modified, were issued in 1216 and 1217 by John's son, King Henry III, who was then still a minor. In 1225, however, when Henry became of age, he issued a third version, which restored most, but not all, of the omitted clauses of the 1215 Charter, and it was this third version of Henry that was confirmed in its exact words by Edward I in 1297.

The document, now in the National Library, is undoubtedly that sent to the Sheriff of Surrey for promulgation in that county. It is believed to have passed from the then Sheriff of Surrey, Robert de Glamorgan, to another branch of the Glamorgan family which lived in Somerset, and many years later, from a member of the family to the King's School. It is written in Latin, very much abbreviated by the use of conventional forms then in use, the text occupying in translation some 3000 words, 15 printed columns in the Statutes. The handwriting is in the clear court hand of Hugh de Iernemuth, one of the Chancery scribes. The seal of white wax, which is appended on plaited silk laces, is one of only a few that exist of "the Seal which was wont to be used in England while the King was in Gascony".

Valuable documents of this kind are very susceptible to deterioration, so the Australian scientists have produced a sealed metal and glass box which, it is hoped, will preserve this historical treasure from any further damage.

The animal skin vellum on which the Charter is written is susceptible to moisture and heat, and both the vellum and the ink are susceptible to strong light.

The means of protecting Australia's Magna Carta are similar to the methods developed in America for the preservation of the Declaration of Independence, which is housed in the nation's archives. The 20 inch long by 16·5 inch wide document will be enclosed in a specially sealed glass and metal container in an atmosphere of argon, the inert gas which is used for filling electric light bulbs. The relative humidity of the argon is maintained at 25% to 35%, to minimize the decay of the vellum, and to keep it flexible.

The glass front of the container is covered with a yellow filter to keep out the ultra-violet rays in strong light. This protects the ink from fading.

The principal difficulty was the manufacture of the composite glass and metal container. This involved metallizing the edges of two thick glass panels, which were then soldered to the lead strips which form the sides of the container.

Great care was necessary to ensure that the seal was as near perfect as modern technology can make it, since leakage of air into the capsule would ruin the effort to extend the life of the document.

To allow periodical checks for possible breakdown of the metal-to-glass seal, a leak detector has been built into the container.

Out of the Past.

SMALLPOX IN TASMANIA.[1]

[From the *Australasian Medical Gazette*, July 20, 1903.]

A SENSATION was caused at Launceston on June 22nd by the announcement that smallpox prevailed and that two deaths had occurred. There have been several cases of scarlet fever in the hospital, some ending fatally, but some rumours gained ground consequent upon the death of Nurse Cash (formerly of Melbourne) at the General Hospital, and enquiries elicited the fact that she died from smallpox. How the disease reached Launceston has not yet been explained, but it appears to have been discovered at the end of May. On June 1st a doctor who had been attending a man for apparently German measles ordered him to the hospital, where he developed a rash resembling smallpox, and died two days later. Nurse Cash and another nurse who had been attending Duggan, were afterwards found to be suffering from suspicious symptoms, and were isolated. The latter recovered completely, but Nurse Cash developed smallpox and died. A porter named Johnston at the institution was also attacked with similar symptoms, and the doctors declared his illness to be smallpox modified by vaccination. None of the patients have been out of the State for some time. One of the members of Miller's Empire Company, who travelled by the steamer "Gracchus", has been here for several weeks past, but he reported himself daily to the health officer, and no suspicious symptoms were discovered in him, and the statement made that he might have brought the infection is doubted. Since then a large number of cases of the disease have been reported, with some fatal results.

Special Correspondence.

LONDON LETTER.

[FROM OUR SPECIAL CORRESPONDENT.]

The Accident Problem.

SUDDEN ACCIDENTAL INJURY is one of the most important medical problems of today. In the United Kingdom, no less than 50 people die from accidents every day. Most of these accidents occur in the home (approximately 8000), the next largest number occur on the road (about 7000) and nearly 600 arise from accidents in the factory. Accidents rank high on the list of deaths from all causes, with the serious loss of years of working life in men. This is particularly striking in the mortality of young men. In 1958, 53% of deaths at this age were caused by accidents, two-thirds being motor-cycle accidents. Although no accurate assessment of the cost to the community of all accidents is possible, it is estimated to be about £500,000,000 a year. It has also been stated that injuries at work cause more loss of time than industrial disputes.

The large increase in accidents in recent years has a number of causes: there are far more motor vehicles, capable of far greater speeds, using roads, few of which are designed for modern transport; there are more mechanized appliances and industrial and farm machines not necessarily designed with enough regard for safety; there are more people at work; and finally, more people travel by all forms of transport than formerly.

There is no doubt that the major cause of accidents is the human factor, and that accidents are largely preventable. The prevention of accidents is the most important of all considerations, and but for the efforts of voluntary organizations, such as the Royal Society for the Prevention of Accidents, the accident situation might be much worse. Meanwhile, there remains the need to provide an efficient service for those injured in the many accidents which do occur. It has become increasingly clear that the medical

[1] From the original in the Mitchell Library, Sydney.

services throughout the United Kingdom are inadequate to deal with the growing number of accidents. Under the ægis of the Royal College of Surgeons, an Accident Services Review Committee was set up "to keep under continuing review the accident service of Great Britain and Ireland and to make recommendations". Seventeen medical organizations are represented on the Committee, which has now published an Interim Report.

In this Report, the Committee urges the provision of a comprehensive accident service for the whole country. Hospitals which developed in relation to the requirements of two or three generations ago fail to meet the needs of today. It considers that the main defects of the present system are: (i) absence of regional organization and coordination; (ii) too many small departments struggling to provide a casualty service; (iii) inadequate reception and waiting accommodation, lack of minor operating rooms and access to special departments; (iv) shortage of sufficiently experienced medical, nursing and auxiliary staff.

During the last 10 years hospital services have been generally improved, but in many instances, the casualty department remains the Cinderella of the hospital service. Far too many small departments are trying to provide a casualty service. The Committee urges that there should be a twenty-four hour service to deal with casualties. This could not be provided at every hospital, but could be provided by suitable designations of hospitals, and by grouping and pooling of resources.

By dividing the country into "accident service areas", a number of self-contained comprehensive services should be organized. Each area would have as its hub a central accident unit, supported by accident units, and would serve a population of about 1,500,000. The three-tiered scheme for each area would consist of a central accident unit, several accident units and a peripheral casualty service, with an efficient ambulance service. Helicopters may be needed in some areas.

The first task would be the establishment of the central ambulance units throughout the country. Details of the functions and organization of the three separate tiers of the proposed service are given in the Report.

In discussing the peripheral casualty service, the Committee calls on all able-bodied, intelligent persons to learn first aid and enrol their names on a list of those willing to give their services when called upon.

Referring to the training of doctors, the Committee states that the medical student should receive more than the few weeks of surgical dressership in the casualty department, which is the present practice, and that this should be replaced by an intensive study of trauma for three months. After graduation, all surgeons should spend at least six months in an accident unit. It is hoped that the Royal Colleges and Corporations will review their requirements for the fellowship to ensure that every surgeon spends adequate time in the study of trauma. The Committee is not in favour of the appointment of "accident surgeons" as a separate specialty.

Future reports of this Committee intend to deal with accident prevention, major disasters, special types of injury and rehabilitation.

Brain Surgery.

Since the introduction in 1935 of the surgical treatment of certain forms of mental illness by leucotomy, some 12,000 such operations were performed in the psychiatric hospitals in England and Wales up to the end of 1954. A survey of the results has been published this year by the Ministry of Health. It was thought that an inquiry designed to ascertain how such patients fared after operation might give useful indications as to the kind of mental disorder amenable to surgical treatment and the kind of result which might be expected. Dr. Godber, Chief Medical Officer of the Ministry of Health, states that "the results cannot afford a measure of the value of leucotomy nor are they intended to be used as a comparison with other methods of treatment, particularly, by the new drugs now available. They do convey a general idea of what has happened to those patients suffering from different forms of mental derangement who had a leucotomy operation in the period covered".

The proportion of patients in the main diagnostic groups were 64% schizophrenics, 25% affective and 11% other diagnoses. Women exceeded men in the proportion of 3:2, women predominating in each of the diagnostic groups. Of all patients, 36% were under the age of 35 years, 60% were aged between 35 and 64 and 4% were aged 65 or over, at the time of operation.

During the years covered by the survey, the standard type of operation was most commonly used in the majority of cases; in a small proportion, the more recent techniques were employed.

It was found that 36% of men and 44% of women were said to have been at least greatly improved after operation, 2% were worse and 4% of men and 3% of women died, death being due wholly or partly to the operation. In accordance with expectation, improvement was most marked among the affective group and least among schizophrenics.

Mass Miniature Radiography.

The Mass Radiography Service using miniature films began in 1943. By 1959, there were 85 units in service all over Great Britain, and in that year over 3,500,000 examinations were made. A statistical analysis of the results of examinations carried out during the three years 1955-1957 relating to more than 10,500,000 examinations is now available.

The persons examined have been broadly divided into two main groups—those referred by their own doctors, and the remainder, termed "public examinees" (that is, persons who volunteered for examination by the units). A 10% sample of all the examinations was analysed by sex, age, social class, occupation, area of residence, medical history and diseases discovered.

During the period 1955-1957, 20,501 new cases of active respiratory tuberculosis were diagnosed, equivalent to two per thousand examined. During the same period, over 95,000 cases of respiratory tuberculosis were notified to medical officers of health, so that nearly 22% of all notifications of the disease were made as a result of mass miniature radiography. Most of these cases were diagnosed while the examinee was symptomless.

In the "public examinee" group, the highest proportion of those radiologically examined was in the young age groups (15 to 25 years). Among all examinees, active tuberculosis was higher in girls and young women than in males of the same age, but above 35 years, the rate for men was higher.

Those socio-economic groups which showed a low prevalence of tuberculosis among men were the agriculture, professional and administrative group and the foreman. High figures were returned for shop assistants, personal-service workers and unskilled manual labourers. Two occupations in the personal service group among males showed an exceptionally high rate—kitchen hands and publicans and barmen.

Apart from tuberculosis, other conditions of the heart and lungs were diagnosed with the aid of miniature radiography. Nearly 5000 cases of cancer of the lung were discovered between 1955 and 1957.

This detailed study should be of value to research workers and those interested in respiratory tuberculosis and other chest diseases.

Correspondence.

THE USE OF UNMODIFIED BLOOD GIVEN BY DIRECT TRANSFUSION.

SIR: I would like to congratulate Dr. McLean on his very stimulating article entitled "The Use of Unmodified Blood Given by Direct Transfusion", which appeared in the Journal of June 24. While the initial requirements for blood in cases of emergency will in the present state of development have to be borne by the blood banks, there are many non-urgent cases in which the use of unmodified blood is undoubtedly better than that which has been stored.

As the blood is transfused very fast, it is essential to be absolutely sure that it is compatible, and I would be interested to know what test Dr. McLean favours. For the past 15 years it has been my custom to cross-match the patient's undiluted serum with the donor's cells suspended in his serum. This mixture is incubated at 37° C. for 30 minutes, and read in the first instance after five minutes and subsequently after half an hour. By this method I have been able to demonstrate the presence of Anti-M, Lewis b, Kell, P and Rh antibodies, though some of these react better at low temperatures. Other tests are done if the history suggests they are necessary.

Recently I received a bottle of blood from the Red Cross Blood Bank labelled "Group O Rh Negative" for a group O Rh-negative female patient who was in a state of shock. After the first five minutes reading the bottle was found to be incompatible, and on investigation it was found to have been obtained from a blood Group A Rh-positive donor. The medico-legal implications of this are far-reaching. The doctor who administers the blood is responsible for its safety, and it is therefore essential that he do the compatibility tests himself or have them performed by an employee financed by him. In the case of doctors employed whole-time by a hospital, the compatibility tests should be done by staff paid by the same organization. Only in this way can responsibility be fixed.

With regard to citrate intoxication, I have administered 18 bottles of blood to one patient and to another patient 20 bottles of blood. Each patient received his transfusion over a period of approximately one hour. Neither patient exhibited citrate intoxication, and both recovered. On another occasion a patient with cirrhosis of the liver was observed to have citrate intoxication after receiving only two bottles of blood rapidly in the theatre.

Yours, etc.,

J. C. A. DIQUE.

Ballow Chambers,
Wickham Terrace,
Brisbane.
July 31, 1961.

THE HYPERVENTILATION SYNDROME.

SIR: Many of us must wish that we had as much faith in the accuracy of our diagnosis as Dr. Barry Christophers (MED. J. AUST., July 15, 1961) and Dr. Carl Radeski (MED. J. AUST., July 29, 1961) have when they make a diagnosis of the hyperventilation syndrome with such ease. Yet, if their reasoning is beset with fallacies—though no one denies that some people overbreathe and need an explanation—they are to be commended for their confident handling of patients whose symptoms (see Dr. Radeski's advice to practitioners at the end of his letter), while obliging us to exclude major disease if we could, would proclaim to most of us that they were neurotic and suggestible people.

How often have symptoms been raised to the status of syndrome or even of disease! And how often has he who is in no hurry to be in the latest fashion felt himself to be gently rebuked (some must have that feeling when they read Dr. Radeski's letter) for his obstinacy or lack of perspicacity!

Yours, etc.,

GERALD C. MOSS.

48A Irvine Street,
Peppermint Grove,
Western Australia.
August 4, 1961.

THE COMPOSITION OF FLUIDS FOR THE CARE OF PATIENTS WITH ABNORMAL ELECTROLYTE SITUATIONS.

SIR: We must take vehement exception to the maintenance fluid requirements for complete anurics as recommended by Dr. Donald Cheek in your Journal of July 29, 1961. The prescription of fluid intake according to his graph would lead to over-hydration—and over-hydration is one of the commonest and most dangerous iatrogenic hazards in the treatment of patients with oliguric renal failure.

The correct, desirable, basic fluid requirement of uncomplicated adult anurics is about 400 ml. per day, and *not* one litre per day. To give this seemingly small allowance is the standard modern practice of all major groups dealing with anuric patients throughout the world; its validity has been amply demonstrated in our own experience of over 175 cases; and its justification has been proved in our research work.

It is true that an adult anuric might be losing 800 ml. or more of water per day by evaporation; but what is frequently overlooked is the fact that there is being added to the circulation each day some 200 ml. of water produced by metabolism of food or flesh and 200 ml. or so of cellular water released when protein is catabolized. The net result is a basic daily requirement of about 400 ml. The actual amount of fluid which should be given to the patient is the basic requirement plus any measurable losses in urine, fæces, vomitus or aspirated secretions. Furthermore, it must be remembered that if the patient is eating, a considerable amount of the basic water requirement may be present in the food. In a typical case the food may contain 300 ml. of water and the additional water allowed would be only 100 ml.

The basic requirement naturally varies with body size and is greater in hot conditions and when the patient is febrile. It also depends on the severity of the uræmia. When uræmia is developing rapidly, the water requirement is less. For the same reason, the water requirement is less in starvation than when the patient is fed.

This subject is to be dealt with fully in an article which is in preparation for publication. The principal conclusion is that the average basic daily water requirement of anurics ranges from about 200 ml. for a child of two years to 400 ml. for an adult.

Yours, etc.,

B. C. E. ASHLEY,
K. D. G. EDWARDS,
J. K. HEALY,
D. JEREMY,
H. M. WHYTE.

Kanematsu Memorial Institute,
Sydney Hospital,
Sydney.
August 2, 1961.

SIR: I was very interested to read Dr. Cheek's article describing the use of a variety of intravenous solutions in abnormal electrolyte situations. There are a few comments I would like to make, with particular reference to problems in the adult patient.

It is a common observation that patients admitted to hospital with a variety of diseases show a relatively normal serum sodium on admission, but subsequently hyponatræmia develops in hospital. In patients in the medical wards, this is usually a primary water excess, sometimes with an over-all salt deficit, but the latter is often of minor degree. The cause of the hyponatræmia is usually administration of excess water, either by forced "free fluids" or by intravenous administration of dextrose in water, or hypotonic saline.

Hyponatræmia is particularly likely to occur in chronic renal failure with a mild salt-losing tendency, when the patient is given three or four litres daily of hypotonic saline or salt-free water. Salt depletion in chronic renal disease is often associated with inability to excrete a large water load promptly, as in Addison's disease, if the glomular filtration rate is low. Water intoxication may occur for this reason in chronic renal disease when a very high water intake is maintained, in the hope that this may improve the excretion of urea. A urine volume of 1 to 2 litres daily does not guarantee that the patient can excrete 3 to 4 litres if the intake is high. In patients wth renal failure, and seemingly adequate urine volumes, water intoxication may occur on a high intravenous intake of hypotonic fluids, and the urine volume may fall, coincident with the falling serum sodium, to anuric levels, as happened in two patients seen recently.

One practical hazard in intravenous therapy is the continuation of oral fluid intake in a patient being given two to three litres a day as a maintenance requirement. The extra fluid will accentuate the over-all hypotonicity of the usual maintenance fluids, with progressive hyponatræmia. It is in wasted, elderly patients with an already expanded extracellular volume that this dilutional hyponatræmia most often and most readily occurs, the wasting of chronic illness being readily mistaken for evidence of dehydration. In this group obligatory solute excretion may be low, and although renal concentrating ability is often impaired, the water required to accompany solute in the urine may be overestimated.

In the calculation of maintenance fluid requirements in sick elderly patients, more emphasis should be based on serial body weights, a practice more accepted in pædiatric circles, taking into account the readiness with which œdema occurs with saline over-administration, and hypotonicity with excess water loading.

With reference to the maintenance water requirements in anuric patients, Dr. Cheek's figure of 1000 ml. daily seems excessive in most patients, and will not allow the required 0·3 to 0·4 kg. daily weight loss which these patients should

show. Dilutional hyponatræmia is common in anuria, and 400 ml. daily is a more suitable daily intake, restricted still further if the patient's serum sodium is abnormally low.

In the treatment of water intoxication, the theoretical amount of hypertonic saline required, as Dr. Cheek says, must be calculated on the basis of total body weight and the difference between the actual and desirable serum sodium level. However, as these patients may have an associated total body sodium excess, the administration of this calculated amount over twelve hours or so may cause acute pulmonary œdema. It is probably preferable to give sufficient 3% saline to increase the serum sodium to 125 mEq/l., which will usually correct the neurological abnormalities of water intoxication. It is important to rigidly limit oral fluid intake over this period, this restriction being continued until the serum sodium is in a more normal range.

These comments, of course, do not apply to the problem of the correction of severe hypotonic dehydration with large sodium losses, in which large amounts of hypertonic saline are urgently required, as Dr. Cheek indicates. They are rather meant to indicate that hyponatræmia is not synonymous with sodium depletion, but merely reflects the balance between sodium and water, and secondly that many cases in the medical wards, without frank losses of sodium and water, have a iatrogenic origin.

Finally, I would like to congratulate Dr. Cheek on his presentation, emphasizing accurate assessment and replacement of fluid and electrolyte deficits.

Yours, etc.,

Department of Medicine,
St. Vincent's Hospital,
Fitzroy,
Victoria.
August 4, 1961.

J. F. NIALL,

PHYSICIAN, PROTECT THYSELF!

SIR: With regard to Mr. J. C. Lane's letter in your issue of July 22, 1961 ("Physician, Protect Thyself!"), he may be interested to hear that no less than 66% of the surgeons in the Northern Territory have fitted their cars with safety belts. We both feel this is an essential safety measure.

Yours, etc.,

Darwin Hospital,
P.O. Box 95,
Darwin,
Northern Territory.
August 1, 1961.

A. F. BROMWICH, F.R.C.S.

AN AUSTRALIAN MEDICAL ASSOCIATION.

SIR: I feel that it is an opportune time to write in support of the Federal President, the Federal General Secretary and the Federal and State Councillors concerning the inauguration of the Australian Medical Association in the new year. Several letters have appeared in the correspondence columns of THE MEDICAL JOURNAL OF AUSTRALIA recently with regard to referenda and the insertion of certain clauses in the draft constitution.

First: a referendum, in my opinion, would be quite useless, unless voting were compulsory. A referendum would certainly not reflect the majority view of doctors in a busy medical profession, as from past experience we could expect a 20% or at most a 25% vote. The present action of the Councillors is quite legal without a referendum. May I ask the referendum supporters this question: Did the present British Parliament in London seek a referendum vote on a question of great national and world-wide importance, the question of whether or not Britain should negotiate for entry to the European Common Market?

Secondly: the insertion of additional clauses to the Draft Constitution, mainly concerning nationalization of the medical profession. To this Dr. John Hunter has given the complete answer in his letter appearing in THE MEDICAL JOURNAL OF AUSTRALIA of July 29, 1961, and that is "that the inclusion of any particular policy of the Association could in no possible way preclude any present or future Government from introducing legislation in relation to such a policy. The Association once created will have every opportunity to formulate and implement its policy to meet the wishes and the needs of its members"; which, shortly stated, means that whatever is included in the Constitution, members of the profession may have to fight (by non-cooperation) as they did in 1938.

One or two letters in your correspondence columns have gone so far as to ask whether or not the Australian Medical Association is necessary at all? To my mind I am amazed that the Australian Medical Association—i.e., the Australian Medical Parliament—was not inaugurated in 1901 at the same time as the Australian Federal Parliament. We have an Australian Dental Association, an Australian Trained Nurses' Association, an Australian Historical Society, an Australian Navy, etc., etc., etc.; even the Boy Scouts have beaten the doctors by the formation recently of the Australian Boy Scouts Association.

My own feeling is that the Australian medical profession should proclaim its recognition and approval of the great and historic value of the recent work of the Federal President, the Federal General Secretary and the present Federal and State Councillors in the formation of the Australian Medical Association. By their outstanding courage and wisdom they have brought the medical profession of Australia to national adulthood. The magnitude of their achievement is as yet impossible of measurement, it is of much greatness. Their names will go forward to the centuries of the future and receive the justified admiration of doctors yet unborn. Australian medical men may in the new year, and with the Federal President and Federal General Secretary in the vanguard, march in a procession of national pride and dignity in association with and affiliation with members of the Parent Body.

Let us never forget the brilliant leadership and hard work which has created, or will shortly create, the infant Australian Medical Association. Our leaders deserve our unbounded gratitude, so let us for the moment deal with the problem of principles; minor details will be dealt with later.

Yours, etc.,

40 Arnold Street,
Killara,
New South Wales
August 7, 1961.

A. LESLIE WATSON.

Post-Graduate Work.

THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

PROGRAMME FOR SEPTEMBER, 1961.

THE Melbourne Medical Post-Graduate Committee announces that the following courses will be conducted in September, 1961.

Courses for General Practitioners.

Demonstrations at the Eye and Ear Hospital.

Details of the eye and ear, nose and throat demonstrations to be conducted at the Eye and Ear Hospital on Saturday, September 2, were given in the last programme published. They will commence at 9.30 a.m. and continue all morning. All practitioners are invited, without fee.

Pædiatric Post-Graduate Week.

1. The following sessions will be conducted in the Lecture Room at the Royal Children's Hospital, except on Tuesday afternoon, and are intended as a refresher course for general practitioners and school medical officers.

Monday, September 4: 9.30 a.m., symposium, "Acute Respiratory Infections", Dr. H. E. Williams, Dr. W. H. Kitchen, Dr. B. W. Neal and Mr. Ian Jack; 11.15 a.m., "Neonatal Respiratory Distress", Dr. T. G. Maddison; 11.55 a.m., "Current Problems in Osteomyelitis", Mr. R. N. Howard; 2 p.m., case presentations.

Tuesday, September 5: 9.30 a.m., "Common Plastic Conditions in Children", Mr. A. R. Wakefield; 10.15 a.m., "Sequelæ of Head Injury", Mr. R. S. Hooper; 11.15 a.m., symposium, "The Management of the Retarded Child", Professor V. L. Collins and Dr. W. S. Rickards; 2 p.m., visit to Kew Cottages.

Wednesday, September 6: 9.30 a.m., symposium, "Urinary Tract Infection", Mr. F. D. Stephens (chairman), Mr. E.

Durham Smith, Mr. R. Fowler and Dr. M. J. Robinson; 11.15 a.m., "Hip Disease in 1961", Mr. E. E. Price; 11.55 a.m., "Problems of Growth", Dr. H. N. B. Wettenhall; 2 p.m., cardiac demonstration.

Thursday, September 7: 9.30 a.m., "The Use of Radiology in Pædiatrics", Dr. H. G. Hiller; 10.15 a.m., "Hæmolytic Anæmias", Dr. A. Clark; 11.15 a.m., "Dangers of Antibiotic Therapy", Dr. S. W. Williams; 12 noon, "Ingested Foreign Bodies", Mr. P. G. Jones; 2 p.m., case presentations.

2. The second part of the course will be a meeting at the Royal Society Hall, 8 Latrobe Street, Melbourne, and will be a more specialized pædiatric meeting, to which all are welcome.

Friday, September 8: 9.30 a.m., symposium, "Management of Dehydration", Dr. B. W. Neal (chairman), Dr. H. Williams, Dr. J. M. Court, Dr. D. B. Cheek and Mr. E. Durham Smith; 11.15 a.m., surgical papers, Dr. Max Kent, Mr. N. A. Myers, Mr. R. Fowler, Mr. E. Durham Smith and Mr. R. N. Howard; 2 p.m., symposium, "Steroids in Childhood", Professor V. L. Collins, Dr. Bryan Hudson, Dr. H. E. Williams, Dr. R. Kelly and Dr. J. H. Colebatch.

Saturday, September 9: 9.30 a.m., surgical papers, Dr. H. G. Hiller, Mr. Peter Williams, Mr. R. Lowe, Mr. I. Nunn, Mr. J. Solomon and Mr. C. Schneider; 11.15 a.m., symposium, "Epilepsy", Dr. M. J. Robinson, Dr. P. Ebeling and Dr. W. S. Rickards.

The registration fees will be £2 2s. for the first part and £1 1s. for the second, to cover the most of catering.

Gynæcology and Obstetrics.

The medical staff at the Royal Women's Hospital will conduct the following course from September 11 to 22.

Monday, September 11: 9 a.m., registration and tour of hospital, with Dr. J. C. Laver; 10 a.m., "Labour Ward Emergencies", Dr. F. Forster; 11.15 a.m., obstetrical round, with Professor L. Townsend; 1.45 p.m., "Pudendal Block", Dr. K. McCaul; 3 p.m., "The Premature Infant", Dr. J. Glyn White.

Tuesday, September 12: 9 a.m., "Minor Difficulties in the Ante-Natal Period", Dr. P. Jeffery; 11.15 a.m., gynæcological round, with Dr. J. W. Johnstone; 2 p.m., obstetrical and gynæcological quiz, Dr. C. K. Churches and Dr. M. Mackie; 4 p.m., "Microscopic Diagnosis in Gynæcological Pathology", Dr. H. F. Bettinger.

Wednesday, September 13: 9 a.m., obstetrical round, with Dr. R. M. Rome; 11.15 a.m., gynæcological round, with Dr. C. K. Churches; 2 p.m., "Psychosomatic Gynæcology", Dr. D. F. Lawson; 4 p.m., "Anæmia and Pregnancy", Dr. M. Whiteside.

Thursday, September 14: 9 a.m., "The Prevention of Preeclampsia and Management of Hypertension", Professor L. Townsend; 10 a.m., ante-natal clinic, Dr. E. V. Mackay; 1 p.m., obstetrical discussion; 4 p.m., "Sterility", Dr. G. Ley.

Friday, September 15: 9 a.m., "Abortion and Habitual Abortion", Dr. W. J. Rawlings; 11.15 a.m., gynæcological round, with Dr. A. M. Hill; 2 p.m., "Forceps", lecturer to be announced: 4 p.m., gynæcological discussion.

Monday, September 18: 9 a.m., "Dangers at the Third Stage", Dr. M. Mackie; 11.15 a.m., "Prolonged Labour", Dr. J. P. O'Neill; 2.15 p.m., discussion on hormones, Dr. J. W. Johnstone and Dr. W. J. Rawlings; 4.30 p.m., "Anæsthesia in Obstetrics and Gynæcology", Dr. K. McCaul.

Tuesday, September 19: 9 a.m., "Indications for Cæsarean Section", Dr. C. N. De Garis; 11.15 a.m., "Abdominal Hysterectomy", Dr. A. R. Long; 2 p.m., gynæcological outpatients, with Dr. H. B. Hattam; 4 p.m., "Maternal Mortality", Professor L. Townsend.

Wednesday, September 20: 9 a.m., "Assessment of Disproportion", Dr. R. Rome; 10 a.m., ante-natal clinic, with Dr. J. Smibert; 2 p.m., obstetrical and gynæcological quiz, Dr. D. F. Lawson and Dr. C. N. De Garis; 4 p.m., "Infection Control", Dr. J. C. Laver.

Thursday, September 21: 9 a.m., "Rh Immunization", Professor L. Townsend; 11.15 a.m., "Vaginal Repair", Dr. B. Anderson; 1 p.m., obstetrical discussion; 2 p.m., gynæcological out-patients, with Dr. V. E. Hollyock; 4 p.m., "Cancer of the Uterus", by Dr. A. M. Hill.

Friday, September 22: 9 a.m., "Ante-Partum Hæmorrhage", Dr. G. D. Ley; 11.15 a.m., "Neonatal Infections", Dr. K. Campbell; 2 p.m., "Hyaline Membrane", Dr. T. G. Maddison; 3.30 p.m., postscript, with the Dean; 4 p.m., gynæcological discussion.

In addition, there will be normal ward rounds by the honorary medical staff.

The fee for the course is £14 14s. for tuition, payable to the Committee, and £7 10s. per week for board and residence, payable to the hospital. Enrolments should be sent to the Committee by August 28. It will be desirable for those taking part to wear long white coats.

Attention is also directed to the all-day clinical meeting for general practitioners which the Victorian State Committee of the Royal College of Obstetricians and Gynæcologists will hold on Sunday, September 24.

Country Courses.

Mildura.—On Saturday and Sunday, September 16 and 17, at the Mildura Base Hospital, the following course will be given.

Saturday: 2.15 p.m., assembly; 2.30 p.m., "The Management of Backache", Mr. J. C. McNeur; 4 p.m., "The Management of Diabetes", Dr. F. I. R. Martin.

Sunday: 10 a.m., "The Treatment of Dysmenorrhœa, including the Use of Hormones in Gynæcology", Mr. R. Zacharin. The local secretary is Dr. E. Broadfoot, Mildura Base Hospital.

Cancer of the Prostate.

An invitation is extended to all medical practitioners to attend the symposium on carcinoma of the prostate, to be held on Saturday, September 16, 1961, in the Public Lecture Theatre, Arts Building, University of Melbourne. Those wishing to attend should apply to the Committee not later than August 26, 1961. The symposium has been arranged by the Melbourne Medical Post-Graduate Committee in collaboration with the Anti-Cancer Council of Victoria.

Overseas Visitors.

Sir Derrick Dunlop, F.R.S.E., B.A., F.R.C.P. (Edinburgh), F.R.C.P. (London), Professor of Therapeutic and Clinical Medicine in the University of Edinburgh, will visit Melbourne from September 9 to 13. He will lecture at the Royal Australasian College of Surgeons at 8.15 p.m. on Tuesday, September 12, on "Oral Hypoglycæmic Agents".

Dr. Dwight E. Harken, M.D., Associate Clinical Professor of Surgery, at Harvard, will visit Melbourne from September 22 to October 4, and on Monday, September 25, at 8.15 p.m., will lecture in the Medical Society Hall on "Surgical Treatment of Angina and Coronary Artery Disease".

The fees for these lectures are 15s. each, but those who have paid an annual subscription to the Committee are invited without further charge.

Neuropathology.

Dr. Ross Anderson will conduct five lectures in neuropathology suitable for candidates for D.P.M., Part II. These will be held at 7.30 p.m. in the Alfred Hospital Pathology Department, on Tuesdays and Thursdays, August 31 and September 12, 14, 19 and 21.

The fee is £5 5s., and enrolments should be sent to the Committee as soon as possible.

Course in Respiratory Diseases.

Under the ægis of the University Department of Medicine, Royal Melbourne Hospital, a symposium on problems of respiratory failure and its management will be conducted on October 27 and 28, 1961. Full details of the programme will be published shortly.

ADDRESS.

The address of the Melbourne Medical Post-Graduate Committee is 394 Albert Street, East Melbourne, Victoria.

University Intelligence.

UNIVERSITY OF NEW SOUTH WALES.

DR. A. W. STEINBECK, Reader in Medicine at the University of Queensland, has been appointed Associate Professor of Medicine at the University of New South Wales. Dr. Steinbeck, who was educated at the University of Sydney, holds the degrees of M.D. (Sydney) and Ph.D. (London), and is a Member of the Royal College of Physicians and of

The Royal Australasian College of Physicians. After qualifying in 1944 and holding house appointments, he held various research fellowships (including the Anderson Stuart Memorial Research Fellowship and the Marion Clare Reddall Scholarship) of the University of Sydney. He was also a Junior and Senior Fellow of the National Health and Medical Research Council before proceeding overseas, as Post-Graduate Fellow in Medicine of the University of Sydney, to work at Hammersmith Hospital and the Post-graduate Medical School of London, where he worked with Dr. R. I. S. Bayliss. There, he later held the Thompson Scholarship of the Royal College of Physicians. He was appointed Reader in Medicine, University of Queensland, in 1955, and has been an Honorary Senior Visiting Physician to the Brisbane Hospital since then, also Physician to the Metabolic Clinic, Out-patient Department. He is a member of the Medical Research Society, London, the Society for Endocrinology, London, the Endocrine Societies of Australia and U.S.A., and the Christian Medical Fellowship, Great Britain. His published work recently has been mainly about adrenocortical function in Addison's disease and hypo-pituitarism, Cushing's syndrome and pregnancy, based on work carried out in part with grants from the National Health and Medical Research Council. Dr. Steinbeck will continue his work in endocrinology and metabolism at Prince Henry Hospital, Little Bay.

Dr. W. R. Pitney has been appointed Hæmatologist, Department of Pathology, Prince Henry Hospital, and Associate Professor of Hæmatology, Faculty of Medicine, University of New South Wales. Dr. Pitney graduated in 1943 with first-class honours from the Medical School of the University of Melbourne, being awarded the Margaret Ryan Scholarship in Medicine, and sharing the Jamieson Prize in Clinical Medicine. His subsequent qualifications are M.D. (Melbourne), F.R.A.C.P. and M.C.P.A. After holding resident appointments at St. Vincent's Hospital, Melbourne, and serving in the Royal Australian Air Force, Dr. Pitney was Registrar in Pathology at the Royal Hobart Hospital and then Registrar in Hæmatology at the Postgraduate Medical School, London. In 1952, Dr. Pitney was appointed Fellow in Hæmatology and Instructor in Medicine, University of Louisville School of Medicine, Kentucky, U.S.A., returning in 1955 to the Postgraduate Medical School as Assistant Lecturer in Hæmatology. In 1956 he took up his present appointment as hæmatologist at the Royal Perth Hospital, Western Australia. Dr. Pitney has published papers on various subjects including hæmophilia and megaloblastic anæmia, and is particularly interested in the physiology of blood coagulation, the mechanism of megaloblastic anæmia in malabsorption, and the application of radioactive isotopes in hæmatological investigation. He intends taking up his new conjoint appointment early in 1962.

THE UNIVERSITY OF ADELAIDE.

The Shorney Prize.

THE Shorney Prize, established for the purpose of perpetuating the memory of the late Herbert Frank Shorney, M.D., F.R.C.S., Lecturer in Ophthalmology in the University of Adelaide from 1926 to 1933, will be offered for the thirteenth time in 1962, and will be for work in diseases of the ear, nose and throat. The relevant clauses of the Statute are as follows:

3. A post-graduate prize, to be called The Shorney Prize, of the value of £100, shall be awarded to the candidate who in the opinion of the examiners has made the most substantial contribution to knowledge in the subjects of ophthalmology or diseases of the ear, nose and throat.

4. The recipient must be a graduate of an Australian University.

5. The material submitted for the prize may be either a thesis or published work in medical or scientific literature, provided that it shall not have been submitted for examination for a degree, or published, more than five years prior to the closing date of entries for the prize.

6. Each candidate must declare that the work described is his own.

7. The prize shall be offered for competition from time to time as the accumulations of the fund permit.

8. The prize shall be offered at least 12 months before the last day for the receipt of applications.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JULY 22, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	..	..	..	..	..	1	..	2
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	1(1)	..	..	..	..	..	1
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	1	..	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	1	6(5)	2(2)	..	2	..	1	..	12
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	3(3)	1(1)	2(2)	1(1)	..	1	..	8
Encephalitis	..	1(1)	..	1	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	97(49)	70(26)	13(3)	24(13)	1(1)	1	1	3	210
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2	..	..	..	..	..	2
Malaria	..	..	1	1	..	..	..	..	2
Meningococcal Infection	1(1)	..	..	..	..	..	..	..	1
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	2(2)	1	3(2)	..	..	..	..	6
Puerperal Fever	3(1)	..	1	..	..	..	..	..	4
Rubella	..	13(11)	..	1	2(2)	..	..	..	16
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	9(7)	14(7)	3(2)	2(1)	1(1)	1(1)	..	..	30
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	2(1)	..	..	..	2
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	29(15)	18(14)	16(9)	3(3)	2(1)	2(1)	2	..	72
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

9. The prize shall not be awarded on any occasion unless in the opinion of the examiners the material submitted is of sufficient merit.

Applications, accompanied by three copies of the evidence which the candidates wish to submit in support, must reach the undersigned not later than August 31, 1962.

V. A. EDGELOE,
Registrar.

Notes and News.

Sydney Hospital: The Keith Inglis Lecture.

The Keith Inglis Lecture for 1961 will be given on Monday, August 28, 1961, at 8.15 p.m., in the Stawell Hall, 145 Macquarie Street, Sydney. The lecturer will be Sir Macfarlane Burnet, F.R.S., and his subject will be "Auto-immune Disease". Sydney Hospital invites all its friends to attend this lecture, which was established as a memorial to the first director of its Kanematsu Memorial Institute of Pathology.

World Health Organization Advisory Panel on Virus Diseases.

Professor F. J. Fenner, of the John Curtin School of Medical Research, Australian National University, Canberra, has been appointed a member of the WHO Expert Advisory Panel on Virus Diseases.

Atomic Energy Contract for C.S.I.R.O.

The Minister-in-Charge of C.S.I.R.O., Dr. D. A. Cameron, has announced the award of two research contracts to C.S.I.R.O. by the International Atomic Energy Agency. The Agency, which has its headquarters in Vienna, awards a number of these research contracts each year to national institutions in member countries. The first two awards to C.S.I.R.O., valued at $12,000, have been made to research workers in the Organization's Division of Plant Industry in Canberra. Under one contract, a small research team under the leadersip of Dr. J. V. Possingham will study the movement of Strontium 90 from the soil to plants. Strontium 90 is the most important long-lived radioactive product of atomic fission. It is important to understand the means whereby it enters plant material through which it may ultimately reach the human body. Knowledge of the movement of strontium is also helpful in our understanding of plant nutrition. The second contract will provide financial support for a study by Dr. R. D. Brock of the effect of different radiation doses on "mutations" or heritable changes in plants. Radiation has been used at Canberra to induce genetic changes in tomato and tobacco plants (for disease resistance) and subterranean clover (for variation in flowering time). The new project will be aimed at trying to find out how the chances of a mutation occurring are affected by the rate at which a dose of radiation is given.

The International Atomic Energy Agency has also provided funds to allow two Asian scientists to receive training in the Division of Plant Industry at Canberra. The two men, Professor J. Y. Chon, of Chuncon Agricultural College, Korea, and Mr. R. C. Rodriguez, of the University of the Philippines, are both learning techniques of plant irradiation.

Corrigendum.

THE MANAGEMENT OF MALDESCENDED TESTIS.

IN the heading of the paper by Dr. David L. Dey, on page 214 of our issue of August 5, 1961, the letters "C.B.E." were inserted after Dr. Dey's name, owing to an error which arose out of confusion with his distinguished father. We apologize to Dr. Dey for this mistake.

Deaths.

THE following death has been announced:

DUNSTONE.—Leonard John Dunstone, on August 5, 1961, at Malvern, Victoria.

Diary for the Month.

AUGUST 19.—Victorian Branch, B.M.A.: Country Branch Meeting (Geelong).
AUGUST 22.—New South Wales Branch, B.M.A.: Hospitals Committee.
AUGUST 23.—Victorian Branch, B.M.A.: Branch Council.
AUGUST 24.—New South Wales Branch, B.M.A.: Clinical Meeting.
AUGUST 24.—South Australian Branch, B.M.A.: Scientific Meeting.
AUGUST 25.—Queensland Branch, B.M.A.: Council Meeting.
AUGUST 31.—Queensland Branch, B.M.A.: Bancroft Oration.
AUGUST 31.—New South Wales Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 *per annum* within Australia and the British Commonwealth of Nations, and £7 10s. *per annum* within America and foreign countries, payable in advance.